Research Square

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Intestinal Contact of Meconium and Meconium Subfractions Upregulates Serum Interleukin-8 and Endothelin-1

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Abstract

Purpose This study aimed to investigate the systemic measurability of interleukin-8 (IL-8), endothelin-1 (ET-1), and urotensin-2 (UT-2) in a meconium-induced experimental model of intestinal injury to predict future intestinal damage. Methods Thirty-five adult female Wistar rats were randomly assigned to five groups. Intraperitoneal injections were administered daily for five consecutive days. Blood samples were collected at baseline and at 24, 72, and 144 hours. Serum IL-8, ET-1, and UT-2 levels were measured using ELISA. Intestinal injury was assessed histopathologically by measuring serosal thickness. Results All meconium-exposed groups demonstrated significant increases in serosal thickness compared with control and sham ($p<0.05$), with the greatest increased observed in the whole meconium group. Serum IL-8 levels were significantly increased in the lipid soluble subfraction and whole meconium groups. Serum ET-1 levels were significantly increased in the water soluble subfraction and meconium groups. No significant differences were observed in serum UT-2 levels. Conclusion The results of this study demonstrate that IL-8 and ET-1 are robust systemically measurable biomarkers reflecting distinct inflammatory and vasoconstrictive pathways of intestinal injury in gastroschisis. In contrast, UT-2 showed no significant alteration in systemic circulation and may potentially act as a local upstream regulator of ET-1–mediated intestinal injury.

1. Introduction

Intestinal damage (ID) induced by intraamniotic whole meconium, water and lipid soluble meconium subfractions has been well documented experimentally in gastroschisis [1–5]. Previous studies have primarily focused on local mechanisms of intestinal injury, particularly the direct contact effect of meconium on the bowel surface and vasoconstrictive impact of meconium on mesenteric vascular structures [4–11]. Although these mechanisms contribute significantly to intestinal damage, they do not fully elucidate the systemic inflammatory and vascular responses observed in gastroschisis.

Meconium is a complex biological substance containing inflammatory components [12–15]. Among these inflammatory components, interleukin-8 (IL-8) has attracted particular attention due to its high intraamniotic concentrations and its central role in neutrophil chemotaxis. IL-8 has been detected in the amniotic fluid of fetuses with gastroschisis and has been shown to mediate local intestinal injury [14–20]. However, the systemic implications of IL-8 in meconium induced intestinal damage in gastroschisis remain poorly defined, and whether IL-8 can be detected systemically in the circulation has not yet been investigated.

Vasoconstrictive peptides such as Endothelin-1 (ET-1) and Urotensin-2 (UT-2) have been show to play important roles for pulmonary hypertension encountered in meconium aspiration syndrome (MAS), a condition characterized by pronounced systemic vascular responses (21–23). Experimental studies have demonstrated that whole meconium and water soluble subfraction induce vasoconstriction of the superior mesenteric artery (SMA) in gastroschisis [9, 11]. Nevertheless, the specific circulating vasoactive cytokines responsible for meconium induced vasoconstriction in gastroschisis have not yet

been identified, and systemic concentrations of circulating vasoactive cytokines associated with intestinal injury have not been systematically investigated through blood based analyses.

Therefore, the present study aimed to evaluate the effects of whole meconium and meconium subfractions on serum IL-8, ET-1, UT-2 levels and their relationship with intestinal damage. While these mediators have predominantly been investigated in terms of their local effects, this study further aimed to determine whether they can be detected in the systemic circulation through systematic blood analyses and to assess their circulating changes in association with intestinal injury.

2. Materials and Methods

The experimental protocol was approved by the institutional committee on the use of live animals (Approval No: 27/2023) and conducted in accordance with institutional guidelines for the care and use of laboratory animals. The present study was conducted on thirty-five adult female Wistar albino rats aged 3–6 months and weighing 250–300 g. The rats were housed under controlled environmental conditions with a humidity level of 50% and maintained on a 12-hour light / 12-hour dark cycle.

2.1. Obtaining of meconium

Sterile meconium was obtained from 10 healthy term human newborns within 24 hours of post gestation after perianal cleaning with 1% chlorhexidine solution. Meconium samples were pooled and homogenized prior to analysis.

2.2. Preparation of meconium subfractions (water and lipid soluble)

Meconium was dried, sterilized, and then diluted with sterile saline to reach a final concentration of 110 mg/dl (dry weight). The water extract of meconium and lipid extract of meconium were prepared according to the method previously described by Töllöfsrud et al. [21]. These extracts were mixed with sterile saline and 1/400 concentration meconium suspensions were prepared. Solutions and extracts containing meconium were stored at + 4°C during the experiment [21].

There were 5 experimental groups. All intraperitoneal injections were performed once daily for five consecutive days.

Control group (n = 7)

No intervention was done

Sham group (n = 7)

Sterile saline (0.9% NaCl) was injected into the intraperitoneal cavity for 5 days.

Water soluble subfraction group (n = 7)

Water soluble subfraction (1/400 dilution) was injected.

Lipid soluble subfraction group (n = 7)

Lipid soluble subfraction (1/400 dilution) was injected.

Meconium group (n = 7)

Whole meconium (1/400 dilution) was injected.

2.3. Obtaining and evaluating biochemical samples

A 1 cc blood sample was taken each time from the tail vein of the rats before intraperitoneal injections and 24, 72, 144 hours after intraperitoneal injections. The blood samples were collected into EDTA-coated tubes and plasma was separated by centrifugation at 3500 G at 15°C for 10 min. IL-8, ET-1 and UT-2 were measured based on colorimetric sandwich ELISA method using the assay kits of BT-LAB (Shanghai, China), Cusabio (Houston, TX) and Mybiosource (San Diego, CA), respectively. The samples were examined and analyzed by two biochemistry experts in a blind manner.

2.4. Histopathological evaluation

At the end of the experiment, all rats were sacrificed by surgical exsanguination. Peritoneal fluid samples from the rats were cultured in the microbiology laboratory to detect possible bacterial contamination. Following sacrifice, the small and large intestines were harvested for histopathological evaluation. Intestinal specimens were fixed in 10% formaldehyde and subsequently embedded in paraffin. Serosal thickness was assessed by randomly selecting five areas from each specimen and measuring them under light microscopy. All experimental specimens were evaluated independently by two pathologists who were blinded to the study groups.

2.5. Statistical analysis

Data are presented as mean ± standard error of the mean (SEM). Statistical analyses were performed using SPSS version 29 (IBM, Chicago, IL, USA). Normality of the data was assessed using both visual inspection (histograms and plots) and analytical tests. A p value < 0.05 was considered statistically significant.

Two-way analysis of variance was used for statistical comparison of normally distributed data between groups, followed by the Tukey's test for pairwise post-hoc comparisons. Kruskal-Wallis analysis of variance was used to cover the variation between groups that did not comply with normal distribution, and then Mann-Whitney U test with Bonferroni correction was used for pairwise post-hoc comparisons.

3. Results

No bacterial growth was detected in any of the peritoneal fluid sample cultures. Serosal thickness of the control or sham groups were similar. Serosal thickness of the water soluble and lipid soluble subfraction groups were significantly increased compared with the control and sham groups ($p < 0.05$). Serosal thickness of the the lipid soluble subfraction group was significantly increased compared with the water soluble subfraction group ($p < 0.05$) (Table 1). Serosal thickness of the meconium group was significantly increased compared with water soluble and lipid soluble subfraction groups ($p < 0.05$).

Table 1
Serosal thickness of the experimental groups (mean ± SEM)

Groups	**Serosal thickness (μm)**
Control	454.27 ± 22.38
Sham	626.10 ± 51.14
Water soluble subfraction	1065.48 ± 40.19*
Lipid soluble subfraction	1326.42 ± 79.31*†
Meconium	1731.89 ± 114.01*†±
** p < 0.05 compared with control and sham groups*	
† p < 0.05 compared with the water soluble meconium subfraction groups	
± p < 0.05 compared with the lipid soluble meconium subfraction groups	

No significant increase in serum IL-8 levels was detected in the control, sham, and water soluble subfraction groups. Serum IL-8 levels were significantly increased in lipid soluble subfractions and meconium groups. Serum IL-8 levels were increased in the lipid soluble subfraction group at 72 hours and 144 hours. IL-8 levels were increased in the meconium group at 24, 72 and 144 hours. The peak increase regarding serum IL-8 in the lipid soluble subfraction and meconium groups was detected at 72 hours (Table 2).

Table 2
Interleukin-8 levels in the systemic circulation of rats before and after intraperitoneal injection (mean ± SEM)

Groups	Baseline	24 hours	72 hours	144 hours
Control	150.32 ± 13.01	147.59 ± 17.05	151.70 ± 26.79	145.25 ± 18.72
Sham	146.12 ± 13.85	133.02 ± 26.64	141.13 ± 31.16	138.45 ± 23.04
Water soluble subfraction	143.82 ± 14.54	152.78 ± 24.01	163.79 ± 12.98	151.43 ± 24.93
Lipid soluble subfraction	162.61 ± 17.07	189.67 ± 20.30	235.88 ± 21.58*†	200.79 ± 15.73*
Meconium	161.79 ± 6.52	189.84 ± 18.50*	247.19 ± 32.67*†	210.23 ± 30.46*
** p < 0.05 compared with baseline value* † *p < 0.05 compared with 24th hour value*				

No significant increase in serum ET-1 levels was detected in the control, sham and lipid soluble subfraction groups. Serum ET-1 levels were significantly increased in the water soluble subfraction and meconium groups. Serum ET-1 levels were significant increased in the water soluble subfraction group at 24, 72, and 144 hours. In the meconium group, ET-1 levels were significantly increased at 72 and 144 hours. Serum ET-1 levels were significantly increased in the water soluble subfraction and meconium groups at 72 and 144 hours compared with 24 hours (Table 3).

Table 3
Endothelin-1 levels in the systemic circulation of rats before and after intraperitoneal injection (mean ± SEM)

Groups	Baseline	24 hours	72 hours	144 hours
Control	14.08 ± 3.34	17.19 ± 3.04	13.05 ± 1.69	11.89 ± 3.29
Sham	10.98 ± 1.76	11.46 ± 2.56	12.62 ± 2.97	10.95 ± 2.23
Water soluble subfraction	12.26 ± 1.30	17.26 ± 2.43*	25.01 ± 3.13*†	20.38 ± 3.07*
Lipid soluble subfraction	11.95 ± 1.90	15.40 ± 2.92	14.78 ± 2.45	13.37 ± 2.92
Meconium	13.08 ± 2.94	16.24 ± 2.16	22.28 ± 3.75*†	19.14 ± 2.09*
** p < 0.05 compared with baseline value* † *p < 0.05 compared with 24th hour*				

Serum UT-2 levels of the groups were not statistically significantly different (Table 4).

Table 4
Urotensin-2 levels in the systemic circulation of rats before and after intraperitoneal injection (mean ± SEM)

Groups	Baseline	24 hours	72 hours	144 hours
Control	8.83 ± 2.75	8.11 ± 1.69	8.23 ± 3.11	6.74 ± 1.36
Sham	9.31 ± 3.63	8.25 ± 1.55	10.97 ± 3.68	9.26 ± 3.66
Water soluble subfraction	7.43 ± 2.13	4.65 ± 0.61	4.64 ± 0.88	8.51 ± 1.93
Lipid soluble subfraction	7.23 ± 1.56	6.48 ± 1.85	7.17 ± 2.22	6.82 ± 1.73
Meconium	6.65 ± 1.14	4.32 ± 1.46	4.08 ± 1.03	5.14 ± 1.71
No significant difference was detected between the groups.				

4. Discussion

Intraamniotic meconium has been implicated in the development of intestinal damage in gastroschisis [1–6, 15, 21, 24–32]. Meconium contains various pro-inflammatory components, including IL-8, bile acids, and free fatty acids [16, 20]. The lipid soluble subfraction of meconium primarily consists of triglycerides, cholesterol, and free fatty acids, whereas the water-soluble subfraction is mainly composed of bile acids, bile salts, bilirubin, dietary fibers, and inorganic molecules [33–35]. The local effects of intraamniotic meconium and meconium subfractions on intestinal damage have been demonstrated in the chick gastroschisis model. While whole meconium caused the most intestinal damage, the lipid soluble subfraction have been shown to cause more intestinal damage than the water soluble subfraction [10]. We found similar intestinal histopathologic results in the present study.

Amniotic fluid from the fetuses with gastroschisis has been reported to contain significantly elevated levels of IL-8 [16]. IL-8 is a chemotactic and angiogenic cytokine produced by endothelial cells, epithelial cells, T lymphocytes, leukocytes, alveolar macrophages. IL-8 causes inflammation by stimulating neutrophil migration and activation [16, 19, 21]. In studies on MAS, it has been shown that IL-8 is predominantly found in the lipid subfraction of meconium and is associated with lung damage [21]. IL-8 has been shown to be related to the intestinal damage in gastroschisis, but there is no study showing which subfraction is more associated with. In present study, we found that serum IL-8 levels increased in the meconium and the lipid soluble subfraction groups. Meconium and lipid soluble meconium induced serum IL-8 increase peaked at 72 hours in the present study. Whole meconium induced serum IL-8 increase begins at the 24 hours. This situation suggests that another trigger in meconium, other than the lipid soluble subfraction causes the increase in serum IL-8. Studies have shown that UT-2 triggers IL-8 expression, and anti-inflammatory treatments such as cafestol, cannabiol that prevent the increase in UT-2 also reduce IL-8 levels [36–39]. We think that the water soluble meconium subfraction, which has a

proven vasoconstrictor response, increases serum IL-8 by stimulating UT-2, and this is the reason why the serum IL-8 increase is seen earlier in the meconium group.

The pulsatility index of the superior mesenteric artery has been reported to be decreased in fetuses with gastroschisis [7, 40]. Clinical and experimental studies have shown that contact with meconium induces local SMA contractions [9]. It has previously been shown that the vasoconstrictive effect of whole meconium is attributed to the water soluble subfraction [11]. As demonstrated in MAS, intratracheal meconium instillation leads to increased serum ET-1 levels, which is associated with increased pulmonary vascular resistance. ET-1 is the most potent vasoconstrictor peptide, released from endothelial and epithelial cells under stress conditions [41, 42]. ET-1 has endocrine and/or paracrine effects not only on blood vessels but also on non-vascular smooth muscle cells such as oesophagus, stomach, intestines, uterus [42, 43]. Just as it is released from endothelial cells after ischemia caused by low intestinal blood flow, exogenous intravascular infusion of ET-1 also causes intestinal ischemia [44, 46]. ET-1 regulates the motility of the gastrointestinal system from the oesophagus to the rectum, including the biliary tract. Studies in patients with obstructive jaundice and patients with intestinal obstruction have found high serum ET-1 levels [47]. In addition, urinary trypsin inhibitor, which has been reported to preserve intestinal contractility in gastroschisis models, has also been shown to inhibit ET-1 induced smooth muscle contraction [8, 48]. These findings suggest that ET-1 may contribute to local intestinal injury through vasoconstrictive effects. Systemic release of ET-1 may exert broader effects that could play a role in the persistent intestinal hypomotility observed in the postnatal period in gastroschisis. In the present study, we found that serum ET-1 was especially elevated in meconium and the water soluble subfraction groups. The increase in serum ET-1 levels in the meconium and water soluble subfraction groups, which has previously been proven to have a vasoconstrictor effect in experiments on gastroschisis, shows that vasoconstrictor effect is mediated by ET-1. The fact that the serum ET-1 level in the water soluble subfraction increased earlier than in the meconium group may also be due to the UT-2 mediated stimulation of ET-1.

In MAS, UT-2 has shown to cause vasoconstriction on the pulmonary artery similar to ET-1 [49]. UT- 2 is potent vasoconstrictor peptide like ET-1, secreted from endothelial cells under hypoxic conditions [49–52]. UT-2 acts through receptors located in the endothelium, placenta and colonic mucosa [51, 53]. Although UT-2 spreads over a wide area with its receptors, UT-2 is thought to act autocrine and paracrine because UT-2 has localized effects and is at the lower limit of detection in plasma [22, 54]. UT-2 has been reported to be 13-fold more potent vasoconstrictor for the SMA compared with ET-1 [55]. Additionally, there are studies showing that UT-2 increases the expression of IL-8 and ET-1, and anti-inflammatory treatments prevent this increase [36, 37, 52]. In the present study, no significant increase in serum UT-2 levels was detected in any of the experimental groups. We speculate that the occurrence of intestinal injury and elevated systemic ET-1 levels despite stable UT-2 concentrations can be attributed to the predominantly paracrine and autocrine activity of the urotensinergic system within the gastrointestinal tract. The localization of UT-2 and its UT receptor to key components of the intestinal wall supports a role in local homeostatic regulation. Locally released UT-2 promotes ET-1 expression through pathways

involving reactive oxygen species (ROS) generation and epidermal growth factor receptor (EGFR) transactivation [52].

Recent evidence has emphasized the clinical relevance of perinatally accessible biomarkers in predicting disease severity and outcomes in gastroschisis, with particular focus on inflammatory mediators [56]. A systematic review by Arai et al. demonstrated that IL-8 is consistently elevated in amniotic fluid and cord blood and may correlate with adverse clinical outcomes, highlighting its potential as a clinically useful biomarker [56]. However, current biomarker research in gastroschisis remains largely confined to inflammatory pathways, with limited attention to vasoactive mediators involved in intestinal perfusion and ischemia. In this context, our findings extend the existing literature by demonstrating that, in addition to systemic IL-8 elevation, ET-1 is significantly increased, particularly in association with the water soluble meconium subfraction, supporting its role in vasoconstriction-related intestinal injury. Although no systemic increase in UT-2 was detected, its potential local paracrine and autocrine effects may still contribute to intestinal damage.

Taken together, these findings highlight a critical gap in current biomarker research and suggest that the endothelinergic and urotensinergic systems represent underexplored but potentially important pathways in the pathophysiology of gastroschisis associated intestinal injury, with possible implications for future biomarker development and therapeutic targeting.

The main limitation of this study is that paracrine distribution of cytokines could not be determined. Another limitation of the present study is that ROS generation and EGFR transactivation were not directly evaluated and were beyond the scope of the current experimental design.

5. Conclusion

The severity of intestinal damage remains the primary determinant of mortality and morbidity in gastroschisis. While previous studies have predominantly assessed IL-8, ET-1, UT-2 mediators locally, our study systematically evaluated IL-8, ET-1, UT-2 levels in blood samples and their association with intestinal injury. Intestinal damage was associated with IL-8 in the lipid soluble meconium subfraction, whereas vasoconstrictor related injury correlated with ET-1 in the water soluble fraction. Systemic assessment of these mediators in blood samples offers a quantifiable and clinically relevant means to monitor intestinal injury. Additionally, IL-8 and ET-1 may act synergistically within meconium, potentiating intestinal damage beyond that caused by individual subfractions. Despite stable systemic UT-2 levels, its local paracrine and autocrine activity may drive ET-1 elevation and intestinal injury, highlighting the need for further investigation. Finally, further investigations are warranted to delineate the paracrine mechanisms of UT-2 and clarify its role in gastroschisis-associated intestinal injury.

Declarations

Author Contribution

A.B., Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, C.K., Conceptualization, Data curation, Resources, Software, Supervision, Validation, Visualization, O.U., Conceptualization, Data curation, Formal analysis, Funding, acquisition, Investigation, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, O.A., Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, M.Ş., Investigation, Methodology, Project administration, Resources, Ö.G.D., Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, S.A., Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, M.E.U., Investigation, G.H., Writing – original draft, Writing – review & editing, M.O., Writing – original draft, Writing – review & editing, F.M.A., Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

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