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Effect of acrylamide administration on fecal short-chain fatty acids in rats

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Summary

Acrylamide is formed as a result of the Maillard reaction between sugars and proteins at high temperatures during food processing and can impair intestinal permeability. The aim of this study is to investigate the effect of exposure to different doses of acrylamide on short-chain fatty acid (SCFA) levels in Wistar rats. Thus, in the present study, animals were divided into 6 groups of 10 animals each. Examination of SCFA levels at the end of the 15th day showed a statistically significant increase in acetate levels in group 5 and a statistically significant decrease in group 6 compared to the control group. In addition, when propionate and therefore total SCFA levels were examined at the end of the 15th day, a significant decrease was observed in group 6 compared to the control group. At the end of the 15th day, isobutyrate, isovalerate, and total branched-chain fatty acid levels were examined, and a statistically significant increase was observed in group 6 compared to the control group. The decrease in acetic and propionic acid levels at the highest doses, and thus in the total SCFA amount, suggests that acrylamide has negative effects on the intestinal microbiota. Thus, it can be stated that high-dose exposure to acrylamide can damage both intestinal tissues and the intestinal barrier, leading to changes in the intestine-associated metabolites.

Keywords: acrylamide, rat, feces, short-chain fatty acids

Acrylamide (AA), also known as 2-propenamide, is an odorless, crystalline compound of low molecular weight that is highly reactive due to its high-water solubility. The International Agency for Research on Cancer (IARC) included AA in the group of potential human carcinogens, neurotoxicants, and genotoxicants in 1994 (9). Recently, the presence of AA in various foods, such as potatoes, coffee, and biscuits exposed to heat treatment, has been revealed. The European Food Safety Authority (EFSA) reports that daily dietary exposure to AA in adults is 0.4-1.9 µg/kg and can be twice as high in children (28). It has been established that the formation of acrylamide in foods is a result of a reaction known as the Maillard reaction due to the triggering of asparagine, which is the source of the amino group, and a reduction in sugars, such as glucose, maltose and fructose, which are the source of the carbonyl group, with heat (1) On the other hand, it has been reported that the intestinal tract plays a critical role in the absorption of acrylamide (AA) and also functions as an important defense barrier (26). Thus, short-chain fatty acids (SCFAs) produced by the intestinal microbiota as a result of the consumption of fiber-rich foods are largely assimilated by intestinal epithelial cells and the remaining ones are excreted in the feces, and SCFA concentrations are mainly regulated by the intestinal microbiota (3).

SCFAs are saturated short-chain fatty acids containing less than six carbon atoms, including acetic acid, propionic acid, butyric, acid, valerate, and hexanoate. Although most SCFA species can be produced in the colon, acetate (C2), propionate (C3), and butyrate (C4) are the most common SCFAs released by certain gut microbiomes that ferment cellulose and starch. Acetate, the most abundant SCFA in both the colon and peripheral circulation, accounts for 60-75% of total SCFAs. SCFAs can be produced naturally by the metabolic pathway, especially in the liver, but the main organ that produces SCFAs is the colon. The main reason why the rates of acetate, propionate, and butyrate are different is the catabolism of different bacteria, as each SCFA is produced through bacterial

fermentation (5, 14, 19, 24). The total SCFA concentration in the colonic lumen gradually decreases from the proximal end to the distal end. The amount and relative rate of each SCFA varies depending on diet, microbiota composition, and expression of transporters. It is clear that SCFAs derived from microorganisms play a role in determining the health of the host (14). The production of SCFAs is followed by absorption into the mucosal epithelium of the cecum and colon, a very efficient process that absorbs about 90-95% of the total yield. Once absorption has occurred, colonic epithelial cells use butyrate as a metabolic substrate to provide energy for themselves, which accounts for 60-70% of the energy requirements of isolated colonic epithelial cells. Only small amounts of colon-derived SCFAs (approximately 36% of acetic acid, 9% of propionic acid, and 2% of butyric acid) are present in the bloodstream and are transported to other tissues in the body, mediating a wide range of biological functions, including host metabolism, immune regulation, and appetite regulation (18). Acetate is produced mainly by anaerobic bacteria that digest dietary fiber, in the animal colon. Propionate production is carried out by a relatively small number of bacterial genera. Propionate is absorbed from the intestinal tract into the portal vein and metabolized in the liver and is found only in low concentrations in the peripheral circulation. Despite its low peripheral concentration, propionate indirectly affects peripheral organs by activating hormonal and nervous systems (5, 27). Propionate may lower levels of apoptosis of intestinal epithelial cells caused by oxidative stress. Propionate has also been shown to support colon homeostasis and health. Some microorganisms in the intestines can synthesize butyrate from lactate and acetate, which prevents lactic acid accumulation and stabilizes the intestinal environment. Butyrate is the preferred energy source for colon cells, and it is estimated that up to 95% of microbially produced butyrate is consumed by the colon, where it plays an important regulatory role in intestinal barrier function and inflammation. Despite low peripheral concentrations, butyrate can indirectly affect physiological functions by activating hormones and the nervous system. Butyrate, the main product of intestinal microbial fermentation, is recognized as an important mediator in the regulation of intestinal microbiota in whole body energy homeostasis (5).

The study by Liu et al. (14) demonstrated that SCFAs, particularly acetate, propionate, and butyrate, prevent intestinal oxidative stress, inflammation, and colon carcinogenesis, and their protective effects on the intestinal barrier have also been proven. Xiong et al. (22) have indicated that SCFAs exhibit various bioactivities, such as anti-inflammatory and immunoregulatory effects.

BCFAs are produced endogenously from branched-chain amino acids by intestinal bacteria in the mammalian body, but their levels are fairly low compared to SCFAs. Moreover, it has been demonstrated that increases in their fecal concentrations may occur with obesity and they may mediate inflammation in adipose tissues (4, 10). Moreover, it was revealed in a similar study that BCFA levels may decrease as a result of dietary intake of fiber foods (20). It is still obvious, however, that the number of studies on BCFAs is limited, and further research is needed on what functions they assume in the living body.

The gastrointestinal tract, the first point of contact between acrylamide in food and the body, is particularly vulnerable to the harmful effects of acrylamide (17). The gastrointestinal tract is the main interface with the external environment. Intestinal barriers effectively protect organisms from the external environment to maintain intestinal homeostasis. During AA transport in the intestine, it is reported that the pH of the lumen affects the passive transport of AA as it moves from the basis to the apex, and higher AA concentrations are reached at pH 6. It is also said that these increasing levels deplete glutathione (GSH) stores. Accordingly, the presence of acrylamide in the intestine poses a significant threat to the intestinal microenvironment. Acrylamide administration may lead to the thinning of the mucus layer by decreasing mRNA expression of mucin 2 and mucus secretion, which impairs the protective function of the intestinal barrier. AA may also disrupt intestinal epithelial tight junctions (TJs) by lowering the levels of claudin, occludin, and ZO-1. This disruption can lead to other hazards, such as pathogenic bacteria crossing the intestinal barrier and infecting cells. SCFAs, mainly acetic acid, butyric acid, and propionic acid, are beneficial for intestinal permeability, as they play a role in the upregulation of TJs (23, 29).

When the literature data were examined, no study was found in which the effect of acrylamide exposure at different doses on short-chain fatty acids and branched chain fatty acids levels in Wistar rats was examined. We hypothesized that escalating doses of acrylamide would dose-dependently alter the SCFA and BCFA profile in Wistar rats. In this context, the present study was conducted to elucidate changes in SCFA and BCFA levels following acrylamide administration at various concentrations and to guide future studies on potential therapeutic agents and pathways.

Material and methods

Study Design. This study was conducted at Selçuk University Experimental Medicine Application and Research Center (SUDAM) and ethical approval dated 30.12.2025 and numbered 2025-117 was obtained from SUDAM.

In the present study, a total of 60 Wistar-Albino male rats (aged 10-12 weeks) were divided into six groups of ten animals each. The acrylamide doses to be applied in the study were determined based on previous experimental studies (6, 8, 12). The term of experiment was planned as 15 days, and the experimental groups were formed as follows. The

animals in the control group (n = 10) were given standard rat feed and drinking water and no experimental treatment was applied. Acrylamide was administered by gastric gavage to acrylamide group 1 (n = 10) at a daily dose of 2.5 mg/kg, acrylamide group 2 (n = 10) at a daily dose of 5 mg/kg, acrylamide group 3 (n = 10) at a daily dose of 10 mg/kg, acrylamide group 4 (n = 10) at a daily dose of 20 mg/kg, and acrylamide group 5 (n = 10) at a daily dose of 40 mg/kg. Three stool sample collections were conducted. The stool samples were collected before the AA administration (day 1), on the 8th day after the administration started (day 8), and on the 15th day, the last day after the administration started (day 15).

Chemicals and reagents. Acetate, propionate, butyrate, iso-valerate, and iso-butyrate were used as external standards, while 4-methylvaleric acid was chosen as internal standard for quantification. All chemicals used in the analyses were obtained from Sigma-Aldrich (Steinheim, Germany) and had analytical purity.

Animals. The study used 60 healthy adult Wistar Albino male rats (340-390 g) obtained from Selçuk University Experimental Medicine Research and Application Center. The animals underwent a 7-day adaptation period before the experiment. Their health was checked by veterinarians. The animals were divided into groups based on statistical analysis to ensure there was no weight difference between them, and there were ten animals in each group. During the study period, the animals were kept in polycarbonate cages at 24 ± 1°C and 60% atmospheric humidity under a 12-hour light/12-hour dark cycle, and they were provided food and water *ad libitum*. The feed was never changed from the beginning to the end of the study. Standard rat feed was used. In its natural state, this feed contains 87.88% dry matter, 9.09% crude ash, 3.51% crude fat, 9.56% crude fiber, and 22.21% crude protein. It provides 2407 ME kcal/kg.

Determination of short-chain fatty acids. The presence and concentration of microbial SCFA (acetic, butyric, propionic) and BCFA (isovaleric and isobutyric acids) in rat feces were determined according to a method described by Bishehsari et al. (2). SCFAs were analyzed by gas chromatography and mass spectrometry (GC, Shimadzu, GC-2030) according to a method defined by Lebet et al. (13) and modified by Tuncil et al., (21). Briefly, samples collected for SCFA and BCFA analysis were combined with 100 µL of internal standard mixture (4-methylvaleric acid). For SCFA and BCFA measurements, frozen samples were brought to room temperature and centrifuged at 13000 rpm for 10 min at +4°C. The supernatants (4 µL) were injected into a GC instrument equipped with a flame ionization detector (GC-FID) and a silica capillary column. The results are expressed in µmol/mg.

Statistical analyses. Statistical analyses were performed using the JMP statistical program, version 10.0 (SAS Institute Inc., Cary, NC, USA). Statistically significant differences between mean values were determined using HSD Tukey multiple comparison tests at a confidence interval of $p < 0.05$. Results are presented as means ± standard deviations. Graphs were created with the GraphPad Prism® Version 8.0 software (GraphPad Software, La Jolla, CA, USA).

Results and discussion

Within the scope of this research, an *in vivo* study was performed to evaluate the effects of acrylamide (AA) on the intestinal microbiota composition and metabolic outputs of rats. Short-chain fatty acids (acetate, propionate, and butyrate) and branched-chain fatty acids (BCFAs; isovalerate and isobutyrate) forming during feeding were measured (Fig. 1, 2). Total SCFA level was calculated based on the sum of acetate, propionate, and butyrate concentrations, while the total BCFA level was calculated as the sum of isovalerate and isobutyrate concentrations. Tables are provided to present differences between days 1, 8, and 15 (Tab. 1 and Tab. 2).

Figure 1 and Table 1 show the distribution of SCFAs in the animals at the beginning of this study. There was no statistical difference ($p > 0.05$) between SCFAs in the groups. This result indicates that a homogenous distribution was observed at the beginning of the study.

When acetate levels were examined at the end of day 15, a statistically significant increase ($p < 0.05$) was

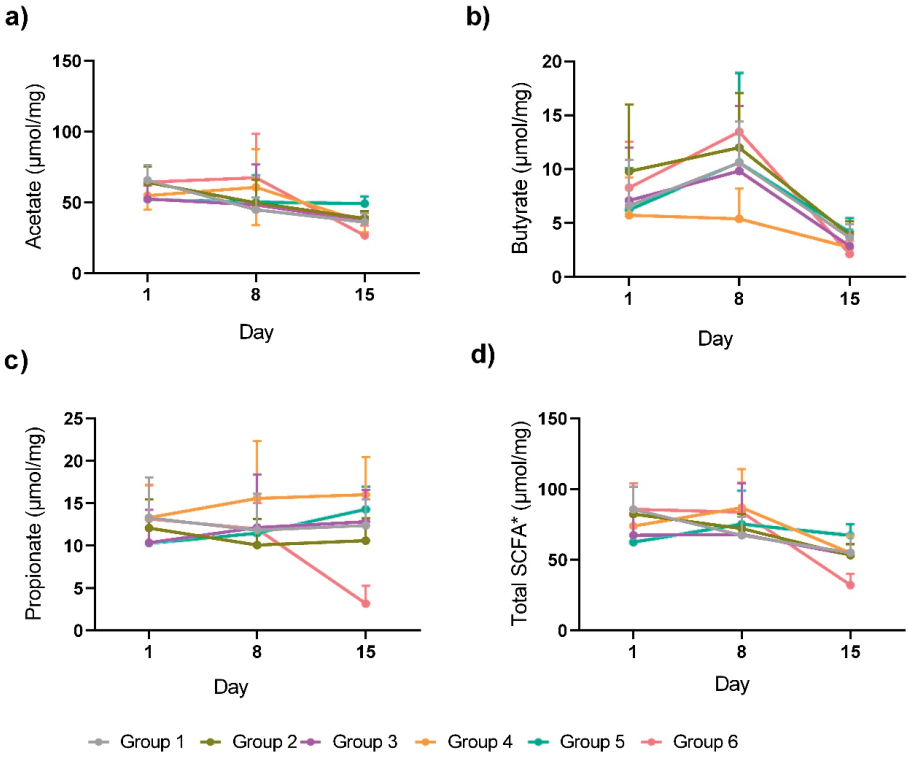

Fig. 1. Amounts of short-chain fatty acids (SCFAs) measured in the feces of rats throughout the study

Explanations: Error bars represent the standard deviation of the mean (n = 10/group). *Total SCFA = acetate + propionate + butyrate. The average mean values are also provided in Table 1.

observed in group 5 compared to the control group, while a statistically significant decrease ($p < 0.05$) was observed in group 6 (Fig. 1, Tab. 1).

At the end of day 15, propionate levels were examined, and a statistically significant decrease ($p < 0.05$) was determined in group 6 compared to the control group (Fig. 1, Tab. 1).

At the end of day 15, SCFA levels were examined, and a statistically significant decrease ($p < 0.05$) was observed in group 6 compared to the control group (Fig. 1, Tab. 1).

When isobutyrate, isovalerate, and BCFA levels were examined at the end of day 15, a statistically significant increase ($p < 0.05$) was observed in group 6 compared to the control group. (Fig. 2, Tab. 2).

The toxicokinetic behaviors of acrylamide have been studied in humans, rats, and mice, and it has been reported that absorption by the gastrointestinal system occurs at high levels following oral administration. It is also important to note that the

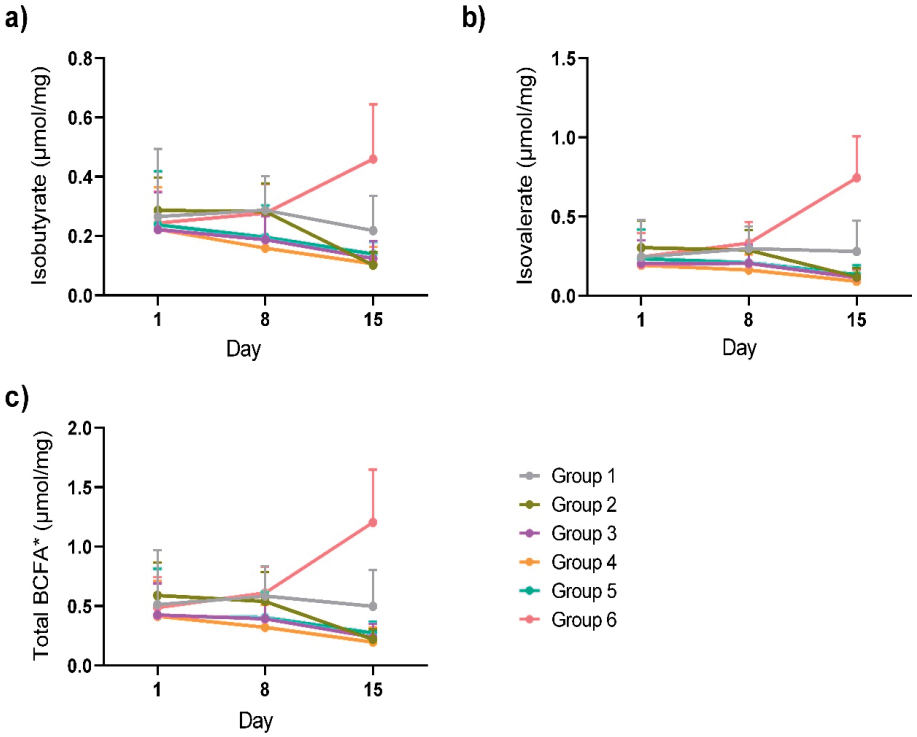

Fig. 2. Amounts of branched-chain fatty acids (BCFAs) measured in the feces of rats throughout the study

Explanations: Error bars represent the standard deviation of the mean (n = 10/group). *Total BCFA = isobutyrate + isovalerate. The average mean values are also provided in Table 2.

Tab. 1. Amounts of acetate, propionate, butyrate, and total SCFA measured in the feces of rats throughout the study

Group	Day 1				Day 8				Day 15			
	Acetate	Propionate	Butyrate	Total SCFA	Acetate	Propionate	Buytrate	Total SCFA	Acetate	Propionate	Butyrate	Total SCFA
1	65.67 ± 10.82^{A}	13.26 ± 4.77^{A}	6.60 ± 4.27^{A}	85.53 ± 15.96^{A}	44.87 ± 8.53^{A}	11.82 ± 4.30^{A}	10.59 ± 3.82^{AB}	67.28 ± 12.96^{A}	36.11 ± 6.34^{B}	12.38 ± 3.08^{AB}	3.65 ± 1.24^{AB}	54.95 ± 13.70^{AB}
2	64.14 ± 11.03^{A}	12.08 ± 3.38^{A}	9.79 ± 6.20^{A}	82.33 ± 19.36^{A}	49.71 ± 16.28^{A}	10.07 ± 3.11^{A}	11.99 ± 5.05^{AB}	72.08 ± 10.36^{A}	38.74 ± 5.19^{B}	10.60 ± 2.67^{B}	3.90 ± 1.28^{AB}	53.17 ± 7.78^{B}
3	52.42 ± 9.52^{A}	10.34 ± 3.87^{A}	7.09 ± 4.88^{A}	67.27 ± 18.18^{A}	48.36 ± 28.39^{A}	12.13 ± 6.23^{A}	9.83 ± 6.02^{AB}	67.98 ± 36.15^{A}	36.79 ± 3.21^{B}	12.81 ± 3.75^{AB}	2.86 ± 1.31^{AB}	53.44 ± 7.56^{B}
4	54.80 ± 9.96^{A}	13.29 ± 3.80^{A}	5.72 ± 3.52^{A}	73.82 ± 11.83^{A}	60.72 ± 26.79^{A}	15.57 ± 6.78^{A}	5.39 ± 2.81^{B}	86.81 ± 27.30^{A}	36.12 ± 6.70^{B}	16.00 ± 4.43^{A}	2.75 ± 0.59^{AB}	54.86 ± 11.35^{AB}
5	52.06 ± 13.26^{A}	10.28 ± 3.11^{A}	6.23 ± 3.89^{A}	62.47 ± 22.32^{A}	50.17 ± 19.06^{A}	11.46 ± 3.99^{A}	10.62 ± 8.29^{AB}	75.16 ± 23.52^{A}	49.18 ± 4.98^{A}	14.29 ± 2.66^{AB}	4.16 ± 1.29^{A}	67.17 ± 7.89^{A}
6	64.26 ± 12.13^{A}	13.16 ± 3.99^{A}	8.27 ± 4.29^{A}	85.70 ± 18.31^{A}	67.46 ± 30.84^{A}	11.96 ± 3.03^{A}	13.46 ± 5.52^{A}	83.70 ± 20.85^{A}	26.69 ± 6.84^{C}	3.18 ± 2.08^{C}	2.14 ± 2.10^{B}	32.02 ± 8.03^{C}

Explanations: $^{A, B, C}$ Different letters indicate statistically significant differences between the groups within each SCFA type; SCFA: Short-chain fatty acids; Total SCFA = acetate + propionate + butyrate

Tab. 2. Amounts of isobutyrate, isovalerate, and total BCFA measured in the feces of rats throughout the study

Group	Day 1			Day 8			Day 15		
	Isobutyrate	Isovalerate	Total BCFA	Isobutyrate	Isovalerate	Total BCFA	Isobutyrate	Isovalerate	Total BCFA
1	0.27 ± 0.23^{A}	0.24 ± 0.23^{A}	0.51 ± 0.46^{A}	0.29 ± 0.11^{A}	0.30 ± 0.14^{AB}	0.58 ± 0.25^{A}	0.22 ± 0.12^{B}	0.30 ± 0.19^{B}	0.50 ± 0.30^{B}
2	0.29 ± 0.11^{A}	0.30 ± 0.17^{A}	0.59 ± 0.27^{A}	0.28 ± 0.10^{A}	0.29 ± 0.13^{AB}	0.54 ± 0.25^{A}	0.10 ± 0.04^{B}	0.12 ± 0.05^{B}	0.22 ± 0.08^{B}
3	0.22 ± 0.12^{A}	0.20 ± 0.15^{A}	0.42 ± 0.27^{A}	0.19 ± 0.08^{A}	0.20 ± 0.12^{AB}	0.39 ± 0.19^{A}	0.12 ± 0.06^{B}	0.11 ± 0.05^{B}	0.24 ± 0.11^{B}
4	0.22 ± 0.14^{A}	0.19 ± 0.16^{A}	0.41 ± 0.30^{A}	0.16 ± 0.11^{A}	0.16 ± 0.10^{B}	0.32 ± 0.19^{A}	0.11 ± 0.06^{B}	0.09 ± 0.07^{B}	0.20 ± 0.12^{B}
5	0.24 ± 0.18^{A}	0.23 ± 0.18^{A}	0.41 ± 0.40^{A}	0.20 ± 0.11^{A}	0.21 ± 0.11^{AB}	0.40 ± 0.21^{A}	0.14 ± 0.04^{B}	0.13 ± 0.06^{B}	0.27 ± 0.10^{B}
6	0.24 ± 0.10^{A}	0.24 ± 0.15^{A}	0.49 ± 0.25^{A}	0.28 ± 0.10^{A}	0.33 ± 0.13^{A}	0.61 ± 0.22^{A}	0.46 ± 0.18^{A}	0.74 ± 0.26^{A}	1.20 ± 0.44^{A}

Explanations: $^{A, B}$ Different letters indicate statistically significant differences between the groups within each BCFA type; BCFA: Branched-chain fatty acids; Total BCFA = isobutyrate + isovalerate

differences in absorption rates may be observed in various species (17). The intestinal mucosal barrier and the intestinal microbiome are believed to act as a defense against various bacteria and their metabolites. It has been reported that, following AA exposure, intestinal permeability is impaired and the flora may trigger inflammation due to a decrease in the number of beneficial microorganisms (7). Yu et al. (25) aimed to elucidate the molecular mechanisms underlying the development and progression of acrylamide-induced colorectal cancer, identify key carcinogenic genes, and investigate their roles in the immune microenvironment and intestinal microbiota. They noted that this relationship is fundamentally based on computational biology approaches and found that *Klebsiella* bacteria, which were frequently found in fecal microbiota samples, mediated the cancer pathway. They also suggested that *in vitro* and *in vivo* experiments, as well as clinical cohort studies, be conducted to comprehensively confirm the causal relationship between acrylamide exposure and colorectal cancer and to further investigate its carcinogenic potential as an environmental risk factor. In another study, Liu et al. (15) exposed mice to 20 µg/mL AA, polystyrene nanoparticles (PS-NPs), and a combination of both in drinking water for 10 weeks and reported that the combined exposure to AA and PS-NPs resulted in more severe adverse effects, such as colon and liver damage, liver metabolic disorders, and intestinal microbiota dysbiosis, compared to exposure to either substance alone. They also reported that the synergistic toxicity caused by AA + PS-NPs would result in a decrease in short-chain fatty acid (SCFA) producing bacteria and an increase in pathogenic bacteria as a result of correlation analysis. SCFAs are reported to help maintain epithelial barrier function on mucosal surfaces, affect the antimicrobial and inflammatory functions of monocytes and macrophages, and have anti-inflammatory and tolerogenic effects on lymphocytes (16). On the other hand, there are only a few studies examining volatile fatty acids levels in fecal samples following AA exposure (19, 25). The present study was conducted to investigate the effect of AA administration at different doses on volatile fatty acids in feces of Wistar rats.

Studies examining SCFA and BCFA levels in the modeling of acrylamide-induced toxicity in experimental animals are limited. In one of the aforementioned studies, the pathogenesis of neuroinflammation resulting from the administration of 40 mg/kg AA to male C57BL/6J mice for 14 days was examined and found to be associated with the gastrointestinal microbiota. In addition, it was determined that the levels of claudin-1 and occludin, which are tight junction proteins responsible for intestinal tissue integrity in the colon, decreased after AA exposure. Analyses of SCFAs in fecal samples revealed significant decreases in acetic acid and propionic acid levels, which were also observed in group 6 receiving the same dose in the current study. Furthermore, it is reported that isovaleric acid levels measured in fecal samples, may trigger an inflammatory response (19), which supports findings of the present study. Yuan et al. (26) reported that in male Sprague Dawley rats, exposure to 30 mg/kg AA over a 1-month period resulted in changes in the intestinal integrity of colon tissue and a significant decreases in propionic acid and acetic acid levels in the cecal content, which is consistent with findings for the highest dose group (group 6) in the present study. They also determined that, although increases in isovaleric and isobutyric acid levels were detected, they were statistically insignificant. In the present study, increases in the levels of the aforementioned branched-chain fatty acids in fecal samples were significant, and it was also observed that individual differences could be observed between rats, especially in BCFA levels. Although it has been reported that there was a decrease in butyric acid levels, the current study found that there was no statistically significant difference between the control group and the acrylamide groups. Furthermore, although the same study indicated that propionic acid and acetic acid levels showed a positive correlation with IL-10, an anti-inflammatory cytokine, it also mentioned the existence of a significant negative correlation between them and pro-inflammatory cytokines. In another study conducted by Guo et al. (11), 20 mg/kg AA was given orally to male mice, and significant decreases in total SCFA levels in the colon were detected at the end of a 4-week period, in parallel with findings of the present study. They also reported decreases in butyrate levels. In the present study, although these levels were lower at the end of day 15, no statistical difference was found compared to the control group. Furthermore, in that study, an increase in acetic acid levels was observed at the end of day 15, as seen in rats exposed to the same dose as group 5 in the current study.

In the present study, acrylamide was found to cause changes in SCFA and BCFA levels in fecal samples only at high doses (groups 5 and 6) and over a prolonged period. It is thought that decreases in the amounts of acetate and propionate may increase the severity of inflammation in the intestinal tissue, and increased levels of fatty acids such as isovalerate from BCFAs may cause inflammation. It was also found that individual differences developed in the levels of BCFAs, especially isobutyrate and isovalerate, in the fecal samples of rats exposed to the highest level of acrylamide. It is believed that such variable individual response may be caused by various factors, such as the individual-specific microbiota, the amount of dietary feed consumed, and varying levels of AA absorption.

Acrylamide disrupts intestinal microbiota, reducing the production of short-chain fatty acids and negatively impacting gut health. The preservation of SCFAs is critical for overall gut and metabolic health. Acetate, propionate, and butyrate, the major SCFAs produced by the intestinal microbiota, attract the attention of

researchers, and there is growing evidence that SCFAs are important mediators that can help prevent and reverse diseases or delay their progression. Endogenous or exogenous SCFA supplementation improves body weight, glucose regulation, and lipid metabolism, as well as prevents inflammation. It is also beneficial for a large number of people with metabolic diseases. Limited information is available on BCFAs, but the present study suggests that elevated BCFA levels may also negatively affect intestinal health. According to the study results, high doses of AA exposure may damage both intestinal tissues and the intestinal barrier, leading to changes in gut-associated metabolites. More clinical studies are needed to investigate the mechanisms of changes in SCFAs in disease states or under high-dose exposure to substances such as acrylamide.

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