pISSN 1229-1153 / eISSN 2465-9223 *J. Food Hyg. Saf.*
Vol. 35, No. 2, pp. 103~108 (2020)
https://doi.org/10.13103/JFHS.2020.35.2.103

Journal of Food Hygiene and Safety
Available online at http://www.foodhygiene.or.kr

Review

Correlation Between food Processing-Associated Stress Tolerance and Antimicrobial Resistance in Food Pathogens

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(Received February 7, 2020/Revised February 19, 2020/Accepted February 19, 2020)

ABSTRACT - Recently, consumer demand for safe but minimally processed food has rapidly increased. For this reason, many food processing industries are applying hurdle technology to enhance food safety, extend shelf life, and make foods appear minimally processed. Meanwhile, studies have shown that a treatment (stress) meant to inactivate foodborne pathogens may trigger adaptation mechanisms and could even offer cross protection against subsequent treatments. Also, certain routine farm practices such as antibiotic and herbicide use could result in the development of antibiotic-resistant pathogens. Such bacteria may be tolerant to food processing-associated stress and be more likely to remain viable in processed foods. In this review, we discuss the correlation between food processing-associated stress and antibiotic resistance. We also discuss molecular mechanisms such as the use of sigma factors, SOS response pathways and efflux pumps as means of cross protection against antimicrobial compounds and other food processing-associated stresses.

Key words: Cross protection, Bacterial adaptation, Promoter sequences, Antimicrobial compound

In recent years, the demand for fresh or minimally processed foods has increased since such foods preserve the quality and physicochemical properties of the food. For this reason, many food companies combine several processing methods (hurdle technology) so as to exert minimal effects on the overall quality of the food while improving the safety and extending the shelf life of the food product. However, some food processing methods occasionally render some pathogenic bacteria resistant to subsequent treatments and even antimicrobial compounds[1]. Also, routine agricultural practices such as herbicide[2] and antibiotic use tend to have significant impact on the susceptibility or resistance of pathogenic bacteria to food processing methods. Throughout the history of modern medicine, the use of antibiotics has been one of the best chemotherapeutic strategies for controlling infectious diseases in humans and farm animals[3]. However, the continuous and indiscriminate use of antibiotics for disease treatment and agriculture has contributed to the development of antibiotic-resistant bacteria as well as increased bacterial resistance in the gut, excreta and the environment[4]. For this reason, antibiotic resistant bacterial infections are rapidly becoming a global health threat and a huge economic burden that require critical measures to combat them[5]. Zoonotic antibiotic-resistant bacteria can be transmitted from livestock (and their products) to humans through food or skin contact[6]. Many studies have suggested that antibiotic resistant gene transfer could occur in the gut between normal commensals and antibiotic-resistant bacteria when foods containing antibiotic-resistant bacteria are consumed (Fig. 1)[7,8]. Since food is usually processed by drying, boiling, heating, frying, freezing, marinating and several other methods, the bacteria in food encounter many physical and chemical stresses (e.g., acids, oxidants, etc)[9]. Although all these processes inactivate pathogens in and on food surfaces, the stresses associated with the processing methods occasionally trigger adaptation responses[10]. This happens as a result of genetic and physiological adjustments in the bacteria could eventually render the cells significantly resistant to other stresses. Moreover, such adaptive responses to food-associated stresses have been reported to have a tendency of conferring cross protection against antibiotics leading to the cells becoming antibiotic resistant[11].

In this review, we discuss the relationship between bacterial stress resistance during food processing and their

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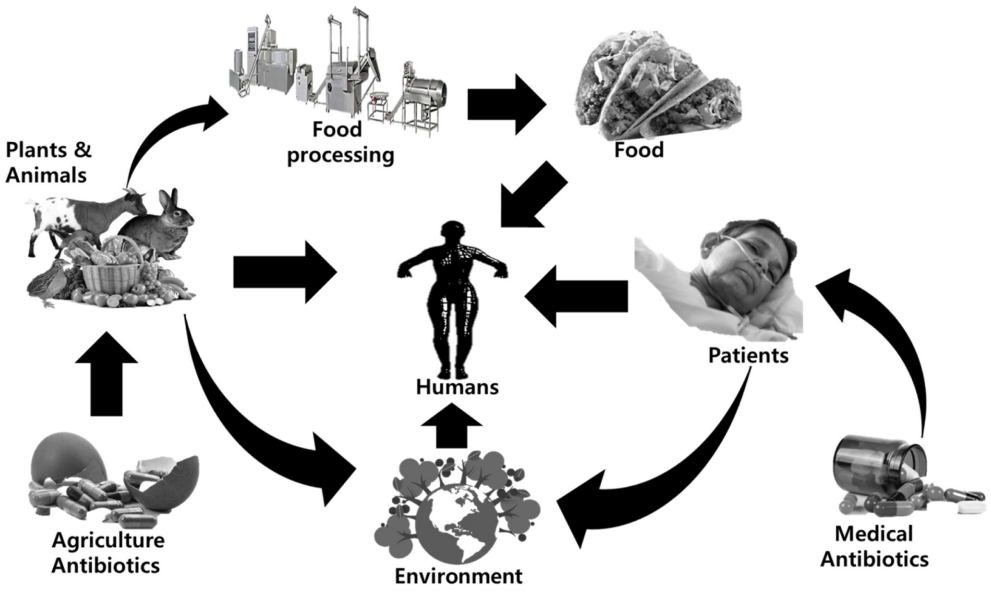

Fig. 1. Examples of how bacteria become antibiotic resistant and how resistant genes are spread.

relationship with antibiotic resistance. We also discuss the molecular mechanisms for the cross protection between food stress and antibiotic resistance.

The interplay between food-associated stress and antibiotic resistance

Bacteria in processed foods usually experience stress resulting from the processing methods and these stresses are intended to inactivate microbial cells.

Osmosis and antibiotic resistance

Salt is a common food preservative for inactivating bacteria, yeast and mold. The addition of salt to foods creates an osmotic gradient between the intracellular and extracellular environments of bacteria cells and this can result in cell death[12]. Although salting is a good method of ensuring microbiological safety, the presence of antibiotic resistant genes in certain bacteria reduce their susceptibility to cell death by high salt concentration. A study by Komora et al.[13] reported that antibiotic resistant *L. monocytogenes* showed high osmotic stress tolerance than their antibiotic susceptible counterparts when they were treated with 37% NaCl for 7 days. Also, they observed that multidrug resistant (MDR) *L. monocytogenes* showed higher resistance to osmotic stress than strains that were resistant to only one antibiotic. Similarly, antibiotic resistant *S. aureus* display better resistance to osmotic stress relative to their susceptible[9]. On the other hand, there are reports that some bacteria develop antibiotic resistance after they become resistant to high salt concentrations. For instance, Al-Nabulsi et al.[14] showed that *L. monocytogenes* displaced resistance to ampicillin, tetracycline, doxycycline and vancomycin after they adapted to high salt concentration. Another study also showed that high salt concentrations could provide cross adaptation for *E. coli* against chloramphenicol and tetracycline[15]. Several bacteria isolated from high salt containing foods[16] and other materials[17] have been reported to be resistant to antibiotics and this demonstrates a possible link between osmotic stress and antibiotic resistance.

Heat tolerance and antibiotic resistance

Thermal pasteurization is a common sterilization method used in food industry as it leads to cell damage. However since high temperatures affect food quality, mild heat (45-60°C) is preferable in food industry[18]. Yet, when microbes are incompletely inactivated, bacteria heat response is triggered and this can affect the efficiency of other treatments. Several reports have shown the impact of thermal adaptation on antibiotic resistance. Ebinesh et al.[19] showed that *Acinetobacter baumannii* developed resistance against norfloxacin, amikacin, tazobactam, piperacillin, imipenem and meropenem after the bacteria were exposed to 45°C. In an earlier study, Rodríguez-Verdugo et al.[20] adapted *E. coli* strains for about 2000 generations at 42.2°C and demonstrated that the heat-adapted strains had become resistance to rifampicin. It however seems that antibiotic resistance does not enhance heat tolerance in bacteria as shown in many studies. For instance Mcmahon et al.[21] have

shown that the survival of MDR *E. coli* (resistant to ceftriaxone, amikacin and nalidixic acid), MDR *Salmonella enterica* serovar Typhimurium (resistant to ceftriaxone, amikacin and trimethoprim) and MDR *Staphylococcus aureus* (ceftriaxone, amikacin and trimethoprim) decreased significantly when stored under 45°C. Other studies found no difference in the D-values of wild type Listeria monocytogenes and streptomycin-resistant counterparts when they were exposed to 55°C[22] and 58°C (for 60 min)[13]. Interestingly, some studies even propose that antimicrobial resistance tends to decrease thermal resistance. For example, Doherty et al.[23] showed that wild type *Yersinia enterocolitica* exhibited better resistance to 50-60°C than their nalidixic acid resistant counterparts. Similarly, MDR *Escherichia coli* O157:H7 displayed a lower D value at 55°C compared to wild types[24].

Cold tolerance and antibiotic resistance

Cooling and freezing exert low temperature stress on microorganisms during food processing and preservation. Freezing cause water in cell membranes to expand, crystalize and destroy the cell membrane and its contents leading to cell death. Meanwhile, bacteria may adapt to cold temperature treatments and this could eventually influence their sensitivity to antibacterial compounds[25]. Exposing *Cronobacter sakazakii* to 5°C for 24 hours drastically improved its resistance to norfloxacin, amikacin, tazobactam, piperacillin, imipenem and meropenem relative to their unstressed counterparts[26]. Similarly, cold treatment of *L. monocytogenes* at 10°C for 24 hours improved their resistance to enrofloxacin, streptomycin, penicillin, gentamycin, tetracycline, doxycycline, ciprofloxacin, vancomycin, and ampicillin[14]. The antibiotic resistance did not disappear after the cold stress was removed.

Acid tolerance and antibiotic resistance

Bacteria may encounter acidic conditions in foods containing organic acids or when the foods are treated with acids. Just as other stresses, bacteria gradually adapt to acidic conditions when they exposed to milder concentrations for some time and this may influence the cell's response to other stress conditions. In a study to ascertain the effect of acid stress tolerance on antibiotic resistance, Al-Nabulsi et al.[14] low pH adapted *L. monocytogenes* (lactic acid, pH 5.5-6.0, 30 minutes) displayed stronger resistance to antibiotics than their acid sensitive counterparts. Another study also reported the possibility of acid tolerance in *Salmonella* species to promote the resistance to ciprofloxacin, ceftriaxone and sulfamethoxazole-trimethoprim[27]. Similarly, acid stressed *A. baumannii* developed resistance against amikacin, norfloxacin, piperacillin-tazobactam, imipenem, and meropenem[19]. Acid adapted *C. sakazakii* also showed strong resistance against tetracycline, tilmicosin, florfenicol, amoxicillin, ampicillin, vancomycin and neomycin, ciprofloxacin, and enrofloxacin better than wild strains[26]. The correlation between antibiotic resistance and acid tolerance has been studied over the years[28]. In an earlier study, wild type *L. monocytogenes* were found to be more susceptible to low pH inactivation when compare to antibiotic resistant strains when they were subjected to 1% lactic acid for 60 min[13]. Similarly, there was an improvement in the acid tolerance of antibiotic resistant *S. aureus* relative to wild type strains after they were exposed to a pH of 1.5 for 40 minutes[9]. Other studies have suggested that pretreatment of some bacteria with antimicrobial compounds could even protect them from subsequent acid stress[29]. Results from studies about the link between antibiotic resistance and acid resistance have yielded contradictory results. For instance, Duffy et al.[24] reported that antibiotic resistant *E. coli* O157:H7 were more easily inactivated in yogurt and low pH juices than wild type *E. coli* O157:H7 strains. Meanwhile, Al-Nabulsi et al.[26] found no difference in acid tolerance between antibiotic resistant and wild type Salmonella strains when exposed to 2% acetic acid and 2% lactic acid. A similar observation was made by Hughes et al.[30] when they treated wild and antibiotic resistant Salmonella species with 3% lactic acid and 100 ppm of acidified NaCl. It is very possible that the impact of antibiotic resistance on acid tolerance as well as the influence of acid tolerance on antibiotic resistance is strain or specie dependent[28].

Mechanisms for cross protection between antibiotic resistance and food-associated stress tolerance

Cross protection of bacteria by food associated stresses could pose danger to consumers. During hurdle technology however, it would be desirable if initial treatments could improve pathogen susceptibility subsequent treatments. For this reason, several studies have been carried out to unveil the mechanisms underlying cross protection between antibiotic resistance and other stress tolerance. Some of the mechanisms include the use of sigma factors, SOS response, and efflux pumps.

Sigma factors

Sigma factors important regulators of stress in bacteria. They play critical roles during cold conditions, heat, acid, salt, oxidative stress and many others[31]. The sigma factors

in Gram-positive are known as σ^S (RpoS) while those in Gram-negative bacteria are called σ^B (SigB)[32].

Sigma factors bind to RNA polymerase core enzymes and directed to DNA promoter sequences to initiate transcription[33]. Deletion of σB in *S. aureus* reduced their resistance to teicoplanin, methicillin, and vancomycin[34] while the presence of sigma factor RpoH heat tolerance and antibiotic resistance in *P. aeruginosa*[35]. Heat shocking of *P. aeruginosa* at 42ºC induced overexpression of RpoH which resulted in the overexpression of the *asrA* gene. *asrA* genes encode aminoglycoside-induced stress response ATP-dependent protease and is responsible for the observed aminoglycoside resistance. It has been shown that pretreating *E. coli* with trimethoprim could deplete adenine nucleotides leading to a drop in intracellular pH. The drop in intracellular pH induces the production of sigma factor-rpoS which also upregulate the production of acid resistant proteins such as GadB and GadC[29]. The rpoS-dependent regulation is critical for increasing intracellular pH and maintaining a constant intracellular pH during acid stress[36]. Since sigma factors are generally triggered into action during stress, the presence of these factors could protect the cell against subsequent stress conditions.

SOS response

The SOS pathway plays a critical role in detecting and repairing DNA damage by expression of genes required for the process[37,38]. LexA (a SOS transcriptional repressor) binds to operator sites of SOS regulated genes to initiate SOS response[39]. In the presence of DNA lesions, RecA (another SOS transcriptional protein) binds to single-stranded DNA causing auto-catalytic cleavage of LexA proteins leading to derepression of SOS genes for DNA repair[40]. The SOS pathway has been shown to be important in bacteria response to ultraviolet radiation, toxic biomolecules, and antibiotics[41]. It has been shown that exposure of *S. aureus* to UV induces DNA damage which evokes the SOS-mediated DNA repair mechanism[38]. The SOS-mediated antibiotic resistance has also been observed in many bacteria including staphylococci[37], *E. coli*[42] and *Pseudomonas aeruginosa*[38]. Since the SOS response is meant to detect and repair DNA damage, it is possible that triggering the SOS response could offer cross protection for the bacterium against subsequent stresses.

Efflux pumps

Efflux pumps are transport proteins critical for transporting toxic compounds out of the cell membrane. Examples of this proton pump families include Multidrug and Toxic-compound Extrusion family, the major facilitator superfamily, the Resistance Nodulation Division family, the ATP-binding cassette superfamily, and the Small Multidrug Resistance family[43]. These transport proteins are stimulated in the presence of stress to actively extrude antimicrobial compounds from microbial cells to resist their lethal effects. For instance, it has been shown that pretreatment of Salmonella Enteritidis with chlorine, sodium nitrite, acetic acid or sodium benzoate can induce the overexpression of marRAB operon which plays a key role in the production of AcrAB efflux pumps[44]. In another study where *E. coli* was exposed to high salt concentration, the cells overexpressed AcrAB-TolC multidrug efflux pumps[15] and this shows how the response to one stress could offer protection against subsequent stresses. Inhibition of efflux pumps has been studied as means of bacteria inactivation. Komora et al.[13] showed that inhibiting efflux pumps with thioriodazine and reserpine in antibiotic resistant *L. monocytogenes* could significantly increase their susceptibility to hydrogen peroxide and benzalkonium chloride. Several studies have shown that deletion of *mdrL* from *L. monocytogenes* could render the cells more susceptible to benzalkonium chloride[1] macrolides and cefotaxime[9].

Conclusion and perspectives

The steps involved in food processing are key means of antibiotic resistant bacteria dissemination. We have shown that the different stresses applied during food processing are potential drivers of antibiotic resistance as well as cross protection promoters. It is therefore important to consider the possibility of cross protection when designing strategies for hurdle technology or other food processing methods. Although the impact of different food-associated stresses on microbes is strain dependent, extensive studies concerning how stress could induce resistance as well as cross protection remains imperative. More so, the possibility of bacteria stresses adaptation and cross protection against subsequent inactivation strategies calls for the development of antimicrobial compounds with multiple mechanisms.

국문 요약

최근 최소한으로 가공된 안전한 식품에 대한 소비자의 수요가 기하급수적으로 증가하고 있다. 이러한 이유로 많은 식품가공 업체에서는 식품안전을 강화하고 유통기한을 연장하기 위한 최소한의 가공공정 중 허들기술(hurdle technology)을 적용하고 있다. 한편, 연구에 따르면 식품에 함유된 병원균을 비활성화하기 위한 공정 및 방법들은 식중독세균들의 스트레스 적응 메커니즘을 촉발시켜

심지어 후속 치료로 부터 교차 보호를 준다. 또한, 항생제와 제초제 사용과 같은 일상적인 농장 관행은 항생제 내성을 가진 병원균의 생성을 초래할 수 있다.

이러한 항생제 내성 박테리아는 식품 처리과정과 관련된 스트레스에 내성을 가질 수 있고 가공 식품에서 생존할 수 있는 가능성을 높일 수 있다. 이 리뷰에서는 식품 가공과 관련된 스트레스와 항생제 내성의 상관관계에 대해 논의한다. 또한, 항균성 화합물 및 기타 식품 처리 관련 스트레스에 대한 교차 보호 수단으로서 시그마 인자(sigma factors), SOS 반응 경로(SOS response pathways) 및 유출 펌프(efflux pumps)의 사용과 같은 분자유전학적 기작에 대해서도 논의한다.

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