J. Microbiol. Biotechnol. (2019), 29(9), 1341–1348
https://doi.org/10.4014/jmb.1905.05060

Review

jmb

Effect of Acetic Acid on Bacteriocin Production by Gram-Positive Bacteria

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Received: May 27, 2019
Revised: July 8, 2019
Accepted: July 20, 2019

First published online
July 23, 2019

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pISSN 1017-7825, eISSN 1738-8872

Acetic acid is indirectly involved in cell center metabolism, and acetic acid metabolism is the core of central metabolism, affecting and regulating the production of bacteriocin. Bacteriocin is a natural food preservative that has been used in the meat and dairy industries and winemaking. In this paper, the effects of acetic acid on bacteriocin produced by Gram-positive bacteria were reviewed. It was found that acetic acid in the undissociated state can diffuse freely through the hydrophobic layer of the membrane and dissociate, affecting the production, yield, and activity of bacteriocin. In particular, the effect of acetic acid on cell membranes is summarized. The link between acetic acid metabolism, quorum sensing, and bacteriocin production mechanisms is also highlighted.

Keywords: Bacteriocin, acetic acid, gram-positive bacteria, acetic acid metabolism, signal molecule

Introduction

Bacteriocin is a small molecule polypeptide with antiseptic and anticancer properties synthesized by ribosomes. Therefore, bacteriocin has good performance in inhibiting the growth of a variety of pathogenic microorganisms and food spoilage bacteria. In the past decade or so, articles on the application of bacteriocins in biomedical fields accounted for most of those published [1], with the majority of these related to the study of bacteriocins produced by Gram-negative bacteria. Bacteriocin research on Gram-positive bacteria is still in its infancy and is mainly concentrated on lactic acid bacteria. It is worth noting that the production of bacteriocin is accompanied by the production of acetic acid [2], indicating that there must be some connection between the metabolism of acetic acid and the production of bacteriocin.

Acetic acid metabolism refers to the cycle and transformation between acetic acid and acetyl-CoA [3], which is ubiquitous in bacterial cells. Many intermediates of acetic acid metabolism such as acetyl-CoA contain both acetyl groups and phosphate groups and are the basis for intracellular material circulation and energy flow. So, acetic acid metabolism is the core link in central metabolism [4] and is closely related to bacterial physiological activities. Bacteriocins can be used as colonizing peptides, anti-microbial or killing peptides and signaling peptides to regulate the ecological function of microorganisms [5]. As agents of anti-competitors, bacteriocins will invade a new community [6]. After successfully establishing its own community, bacteriocin prevents invasion by other species, and regulates population dynamics by regulating intercellular competition [5]. Co-culture induction [7] and the addition of cell-free supernatants [8] increase bacteriocin production. This result validates the ecological function of bacteriocin. Acetic acid metabolism regulates physiological activities in cells, and bacteriocin regulates extracellular physiological activities. The most important thing is that the two are inseparable. In Gram-positive bacteria, many biological traits are regulated by the metabolism of acetic acid such as entering competence [9], biofilm formation [10], bacteriocin production [7], and exhibition of virulence [11]. Bacteria indirectly regulate the production and ecological function of bacteriocins by acetic acid metabolism. This paper

discusses the effects of acetic acid on bacteriocin production by Gram-positive bacteria. It also illustrates the relationship between quorum sensing and acetic acid metabolism, and the impact of the microenvironment on bacteriocin production.

Effects of Acetic Acid on Bacteriocin Production and Activity at Physiological Metabolic Levels

Effects of pH and Acetic Acid Dissociation on the Yield and Activity of Bacteriocin

The classification of bacteriocins is complex and controversial. This article summarizes the classification of bacteriocins according to the ideas of Mr. Eldin Maliyakkal Johnson (Table 1) [12]. Bacteriocin is a metabolite of polypeptide produced by bacteria and has a certain bactericidal effect. The effect of acetic acid on the production and bioactivity of bacteriocin is divided into two aspects. On the one hand, the pH affects the production and bioactivity of bacteriocin. Bacteriocin is produced in a specific pH range, and bacteriocin production is significantly correlated with initial pH [13]. However, the final production pH is almost the same or lower [14]. The literature indicates that bacteriocin is not produced when the final production pH is less than 4.5 [15], and the optimal pH range for production is 6.0–6.5 [15, 16]. The bioactivity of bacteriocin has a broad pH range (Table 1) [17], with some bacteriocins remaining active in acidic and alkaline environments, however, the optimal pH range for their bioactivity is 5–7. Extreme pH will significantly reduce bacteriocin activity [18] because a strong acid or strong alkali environment can affect the spatial structure of

Table 1. Classification and characteristics of bacteriocins.

Bacteriocin class	Structure		Characteristics	Bacteriocin
The Lantibiotics (Class I)	Class I are post-translationally modified peptides (<5 kDa). Extensive post-translational modifications occur in the pro-peptide region in the serine, threonine, and cysteine residues.	Class Ia: linear lantibiotics	Heat stable at 121°C for prolonged heating at pH 2. Become less heat stable at pH 5–7.	Nisin
		Class Ib: globular lantibiotics	Heat stable at 100°C for 60 min. Most stable at acid and neutral pH.	Lacticin 3147A
		Class Ic require two or more modified peptides to be functional.	Resistant to pepsin, proteinase K, a-amylase, and lipase.	Plantaricin C
The unmodified peptides (Class II)	The class II bacteriocins are composed of translationally unmodified small peptides (< 10 kDa).	Class IIa consist of a disulphide bridge formed by cysteine residues at their N- terminal region.	Stable at pH 4 to 6; heat stable at 100°C for 10 min.	Pediocin PA-1
		Class IIb require the aid of two or more non-modified peptides for eliciting antimicrobial activity.	Stable at pH 3 to12; heat stable at 100°C for 60 min.	Enterocin 1071
		Class IIc are single peptide non-pediocin like bacteriocins which are a heterogeneous group	Stable under mild heat conditions and sensitive to proteolytic enzymes.	Enterocin EJ97
Large proteins (Class III)	Class III are large proteinaceous (>30 kDa) heat labile bacteriocins. Their primary structure consists of a binding domain and an N-terminal catalytic domain.	Class IIIa are considered lytic bacteriocins.	Class IIIa attack the peptidoglycan layer of the cell wall in susceptible gram-positive bacterial targets.	Enterolysin A
		Class IIIb are non-lytic, heat-labile bacteriocins.	Class IIIb can hamper the glucose uptake by the cells and starves them and also disturbs the membrane potential.	Helveticin J, Streptococcin A-M57, and Dysgalacticin
Circular peptides (Class IV)	Class IV are cyclic peptides formed by the ligation of their N-terminus to the C-terminus via an amide bond, and they have a molecular weight of 5.5–7.5 kDa		Active at pH 9.0 and in combination with moderate heat treatment. Inactivated when heated for 5 min at 65°C in an alkaline (pH 9.0).	Enterocin AS-48

the protein. Moreover, extreme pH can also destroy the signal molecule structure of bacteriocin, causing a partial loss of function and hindering communication between bacteria. In summary, the production of bacteriocin may be related to both the initial and active pH during bacteriocin production, indicating that pH acts as an important signaling system.

On the other hand, acetic acid as an organic acid, whether it is in a dissociated state affects the production of bacteriocin. When the pH is equal to pKa (acidity coefficient), acetic acid hardly ionizes and can freely diffuse through the cell membrane. When the intracellular pH is high, acetic acid can decompose to release protons and conjugate bases. Acetate is considered to be an inducer of bacteriocin production [19]. A large number of hydrogen ions can destroy the membrane proton kinetics [20], affecting the secretion of bacteriocin. At the same time, the release of protons acidifies the cytoplasm [21]. Acid shock may affect the activity of the electron transport chain and disrupt cell metabolism [22, 23]. In the bacteria, resistance to stress is mainly maintained to ensure intracellular balance [24]. For example, *Bacillus cereus* reduces hydrogen ions in two ways: the first is to pump protons out of the cell, and the mature cell membrane and wall prevent protons from entering the cell. The second method relies on basic compounds, which can counteract the acidification of the cytoplasm, and the decarboxylation of amino acids depletes protons [25], such as glutamate [26], arginine and ornithine.

Effects of Bacterial Cell Growth and Metabolism on Bacteriocin Production under Acetic Acid Conditions

Bacteria can monitor themselves or competitors by signaling molecules. When a signal molecule reaches the concentration threshold, it can initiate the expression of related genes in the bacteria to maintain population stability. Quorum sensing behavior is a relatively common ecological phenomenon. Acetic acid can significantly activate the quorum sensing system, resulting in a decrease in bacterial growth rate. At this time, cell growth and metabolism are slowed down, protein synthesis is reduced, and succinic acid production is reduced [27]. Cells quickly adapt to changing environments by turning off unnecessary metabolism [28], preventing the misexpression of genes, conserving resources and purposefully expressing desired substances. This suggests that acetic acid affects the signaling pathways that control cell division and cellular nutrient diversity [29]. Acetic acid stimulation can also lead to cell growth arrest and even cell death [30]. The rupture of a single cell helps to increase the release of XIP, a sigma factor-inducing peptide [31], thereby increasing the resistance of the bacterial population and regulating the production of bacteriocin. In addition, high concentrations of acetate activate the metabolism of acetic acid, converting acetic acid to acetyl-coenzyme A [32]. The intermediates of acetic acid metabolism promote the activation and transmission of two-component system phosphorylation. In general, under acetic acid conditions, the population will eliminate individuals with poor competitiveness and establish an environmental condition that is not suitable for competitors.

The Effect of Acetic Acid on Cell Membrane Promotes the Production of Bacteriocin

The cell membrane is a semi-permeable membrane that blocks harmful substances from entering the cell and helps the bacteria to survive in adverse environments. Environmental signaling molecules and their threshold concentrations regulate the maturation of cell membranes [33], enhancing or attenuating the perception of a substance. Acetic acid can activate sensor proteins and transmit environmental signals to the cell membrane [34]. When Gram-positive bacteria are stimulated by acetic acid, the cell membrane of the bacteria changes [35]. On the one hand, the cell membrane reduces the permeability to acetic acid, and on the other hand, the maturation of the cell membrane promotes the production and secretion of bacteriocin.

Acetic acid regulates cell membrane maturation. The maturation of cell membranes is largely divided into four steps: surface attachment, microcolony formation, depth of mature cell membranes, and structure of mature cell membranes [36]. The early stage of cell membrane maturation is mainly regulated by acetic acid as a signaling molecule, and the late stage of cell membrane maturation is caused by acetic acid metabolism and quorum sensing. Acetic acid can modify the lipid membrane composition [37], for example, isomerizaton of *cis*-to trans-unsaturated fatty acids, increase of phosphatidylcholine, increase of *cis*-vaccenic acid and formation of capsular polysaccharides. In addition, under acidic conditions (pH = 4), the production of long-chain fatty acids in the cell membrane increases, resulting in a decrease in branching ratio [38]. This leads to a decrease in the hardness, elasticity and fluidity of the cell membrane. Other literature has shown that acetic acid can increase the surface area of the cell membrane, thereby reducing the relative area of passive diffusion of acetic acid into the cell [39], which increases biofilm composition and

complements transcriptional regulation systems [40]. Under acetic acid conditions, the genes involved in cell membrane maturation will also change accordingly, such as *luxS* [41] gene and *agr* [42] gene.

In general, when acetic acid acts on Gram-positive bacteria, the cell membrane is stimulated by acetic acid. The cells begin to respond to the extracellular environment. Thus, cells adapt to adverse environments through mature cell membranes and begin to produce large amounts of bacteriocin to kill competitors or to signal to the population.

Relationship between Induction of Bacteriocin Production and Metabolism of Acetic Acid

The Production Mechanism of Bacteriocin

Bacteriocins are a class of antibacterial peptides or precursor peptides synthesized by bacteria. The synthesis of bacteriocin is strictly regulated, and it is generally synthesized and secreted in the logarithmic growth phase of bacteria and increases secretion as the number of bacteria increases. Next, the mechanism of bacteriocin production by Gram-positive bacteria was reviewed in terms of genomics and proteomics. At present, the research on the mechanism of bacteriocin production by Gram-positive bacteria is more mature for *Streptococcus mutans* and *S. pneumoniae*. There are two mechanisms for the production of bacteriocin, such as *S. mutans* (Fig. 1) [43]. The first is CSP (competence stimulating peptide) signaling that mediates bacteriocin expression. The *comC* expresses a CSP signal peptide. The CSP signal peptide is cleaved and exported by the ComAB protein on the membrane [44]. After extracellular processing, mature CSP phosphorylates ComD. The phosphate group is then delivered to the ComE protein. Phosphorylated ComE protein activates the expression of the bacteriocin gene [43]. The second involves XIP (*sigX*-inducible peptide) signaling which induces bacteriocin synthesis. The *comS* gene expresses an XIP signal peptide which is secreted into the extracellular environment. The extracellular XIP peptide is then reintroduced by Opp permease. The XIP and ComR proteins interact directly to form a complex. This complex then induces transcription of *sigX* (sigma factor). SigX binds to RNA polymerase to activate the expression of the bacteriocin gene [45]. Simultaneously, SigX binds to the 5′ end of the comE gene and induces *comE* transcription, increasing the ComE protein which is a phosphorylated substrate [43]. These indicate that bacteriocin is produced by two regulatory systems. A small amount of CSP can

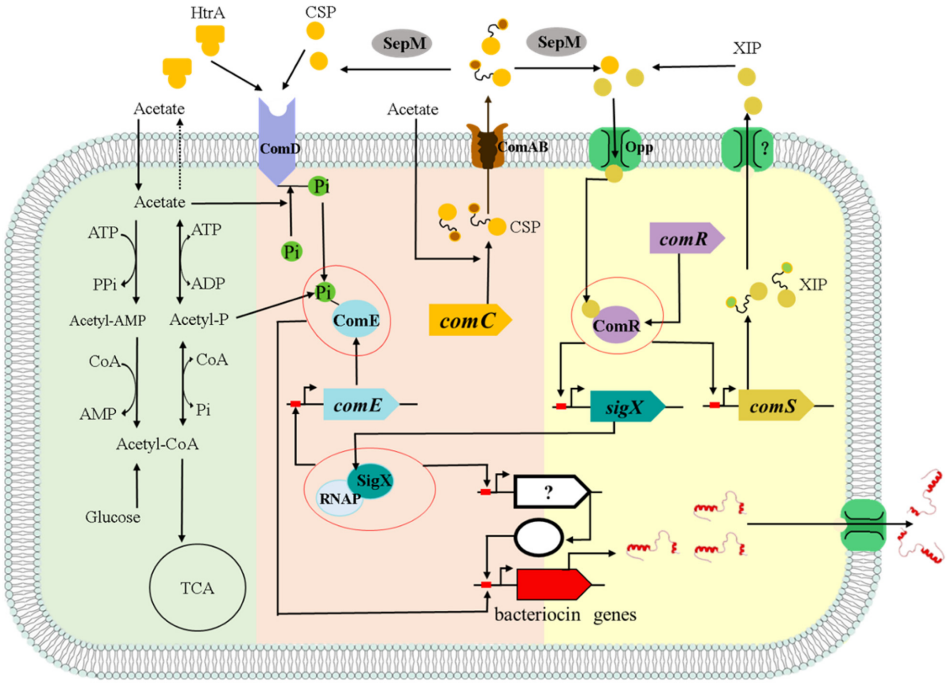

Fig. 1. The mechanism of production of Gram-positive bacteria bacteriocin and the effect of acetic acid on bacteriocin production. The green area represents acetic acid metabolism; the orange area represents the CSP regulatory system; the yellow area represents the XIP regulatory system.

induce the appearance of a single peak of bacteriocin. A large number of CSPs can activate XIP signal induction, and the two signaling molecules together induce the appearance of bacteriocin double peaks.

Both Acetic Acid and Bacteriocin Can Induce Bacteriocin Production

A variety of environmental factors also affect the expression of bacteriocins, such as cell density, nutrient conditions, and acetic acid. The concentration of CSP signaling molecules is critical for the initial effects of bacteriocin production. HtrA serine protease digests CSP peptide pheromone extracellularly, controls the concentration of extracellular CSP, and normally the concentration of extracellular CSP is lower than the threshold concentration that induces bacteriocin production [46]. Another study indicates that HtrA controls the expression of bacteriocin by competing with CSP for the recognition site of the ComD protein in the two-component system [47]. The pH range of HtrA protein activity is between 5.5 and 10.0, so stimulation of acetic acid also attenuates HtrA activity [48]. Under acidic stress, CSP expression can be up-regulated [48]. A large number of CSPs are more likely to compete for recognition sites on ComD, attenuating HtrA inhibition [46]. A change in CSP concentration is a signal of whether a cell is stressed. At high concentrations of CSP, cells not only grow at a slower rate, but high concentrations of CSP can trigger cell autolysis [48]. Cell autolysis can slow down the degree of extracellular pH reduction and weaken competition for nutrients. Acetic acid and acetyl phosphate respectively phosphorylate the ComD protein and the ComE protein to promote bacteriocin expression [49, 50].

Both acetate and bacteriocin are dose-dependent inducers of bacteriocin production [19]. The biosynthesis of bacteriocin is dependent on the extracellular peptide produced by the strain, and bacteriocin can also act as an extracellular regulator of biosynthesis [51]. For example, *Streptococcus* CipB bacteriocin is a bifunctional peptide that combines lytic activity and transcriptional regulation [52]. Bacteriocin can be regulated in both species and populations. Optimal cell growth does not always result in a large production of bacteriocin. In general, low growth rates or adverse conditions may stimulate bacteriocin production [53].

Effect of Acetic Acid on Bacteriocin-Related Plasmids

Under acetic acid treatment, bacteria reduce catabolism, and the plasmid also undergoes a series of altered reactions [54]. Plasmid can regulate the expression of DNA-binding protein genes to achieve the survival and expression of extracellular DNA taken up by cells [55]. Acetic acid can damage DNA and inhibit new DNA synthesis, but it does not immediately cause leakage of intracellular components [56]. Furthermore, under acetic acid treatment, bacterial cells have high levels of purines and pyrimidines, which provides an advantageous environment for plasmid-encoded gene expression [57]. Certain plasmids or DNA can self-transfer within a population to rapidly communicate and respond between bacteria [58]. This is in parallel with the actual conditions required for a large amount of bacteriocin to be produced. Some Gram-positive bacteria produce bacteriocins encoded by plasmids [59], such as the pXO1 plasmid of *B. anthracis* (encoding a putative membrane-bound bacteriocin) [60], and the pWcMBF8-1 plasmid of lactic acid bacteria (a component required for the synthesis of bacteriocin) [61]. Acetic acid at a concentration of 1.0% or higher increases the number of copies of the relevant plasmid, for example, the pGE1 plasmid and the pGE3 plasmid [57], which decompose acetic acid and the pJT2-1 plasmid, which enhance the resistance of acetic acid [62].

Due to their excellent antibacterial properties, bacteriocins have become the most promising alternative to antibiotics and have gradually attracted wider interest in the medical field. More and more scholars are beginning to pay attention to the study of bacteriocins. At present, Gram-positive bacteria bacteriocin research mainly focuses on their transport proteins, bacteriostatic methods, and immune mechanisms. It is worth noting that there are unresolved problems with the bacteriocin production mechanism. For example, it is not known what transporter or system is used to secrete and treat XIP precursors (Fig. 1) [63], and there is no direct evidence that HtrA disrupts ComAB function or that HtrA blocks CSP-induced function [64]. There is a lack of research into the effects of acetic acid on quorum sensing in research progress. The metabolism of acetic acid, which affects bacterial life activities through material circulation and energy flow, is the core of central metabolism. Quorum sensing is a regulatory mechanism through which bacteria evolve under stress. Acetic acid metabolism and quorum sensing are a response of bacteria to environmental changes. But, how bacteria survive in unsuitable environments and how they maintain their population stability, *i.e.*, bacterial physiology and group behavior, are important topics of ecology that require further study.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (31470537), Heilongjiang Provincial Key Laboratory of Plant Genetic Engineering and Biological Fermentation Engineering for Cold Region.

Conflict of Interest

The authors have no financial conflicts of interest to declare.

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