Approcci innovativi all'AMR.

Glicina e batteri: cibo o veleno?

Simona Barnini
AOUP

La prima pagina del lavoro di Wyon e McLeod, che annunciano, nel 1923, l'effetto inibente di alcuni aminoacidi sulla crescita batterica, mentre molti scienziati ne studiano l'effetto opposto.

PRELIMINARY NOTE ON INHIBITION OF BACTERIAL GROWTH BY AMINO-ACIDS[1].

By G. A. WYON, M.D., B.Sc. and J. W. McLEOD, M.B.

(With 2 Charts.)

A good deal of Pasteur's earlier work was carried out with various forms of bouillon prepared from meat, *i.e.* media containing appreciable percentages of amino-acids. Subsequently the percentage of amino-acid in bacteriological media was increased by reinforcements of the meat extract by soluble protein in the form of peptone.

But recently the value of amino-acids, as such, in promoting bacterial growth has been much investigated.

THE INHIBITION BY VARIOUS AGENTS OF THE LYSIS OF *BACTERIUM COLI* BY GLYCINE

By J. GORDON, R. A. HALL and L. H. STICKLAND

The School of Medicine, Leeds

In view of the work of Maculla & Cowles (1948) on the lysis of bacteria by glycine, and of our subsequent work (Gordon, Hall & Stickland, 1951*a*) dealing with the kinetics of the reaction, we thought fresh light might be thrown on the mechanism of the reaction by a study of its inhibition.

This mechanism might conceivably be either a physical one, bringing about rupture of the bacterial membrane by for instance osmotic effects, or a chemical one involving an interaction between glycine and the protein or between the glycine and some enzyme concerned in the lytic process.

Although the exact mode of action is not known, the high temperature coefficient together with the pH relationship of the process, suggests that the action is essentially chemical, presumably enzymic, and that a merely physical action of the high amino-acid concentration on the bacterial membrane is of less, or no, significance. Some evidence was presented also by Gordon, Hall & Stickland (1951*b*) to show that osmosis alone is not enough to account for the lysis by glycine. Many substances are known which can bring about changes in the bacterial

(a) *The relationship between the time of incubation with glycine and the degree of lysis*

Using the technique described, samples of bacterial suspensions were incubated with 1·0M-glycine at 37° C. for varying periods of time. The degree of lysis followed the course shown in Fig. 1 for this concentration of glycine.

KINETICS OF THE LYSIS OF *BACTERIUM COLI* BY GLYCINE

By J. GORDON, R. A. HALL AND L. H. STICKLAND
From the School of Medicine, Leeds 2

(With 4 Figures in the Text)

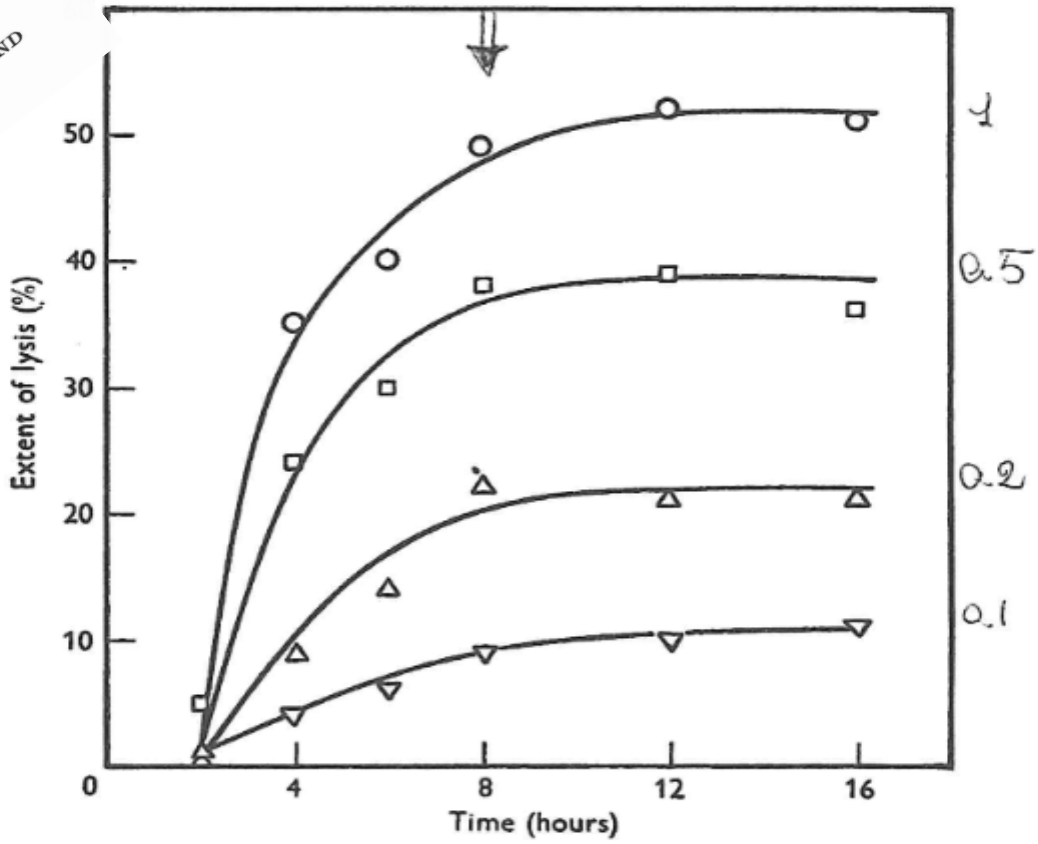

Fig. 1. The course of lysis at different glycine concentrations, at pH 7·5 and 37°. *Bact. coli*, strain 8, was used. ○——○, 1·0M-glycine; □——□, 0·5M-glycine; △——△, 0·2M-glycine; ▽——▽, 0·1M-glycine.

In this experiment there was a delay of 2 hr. during which practically no lysis occurred, followed by a rapid lysis which reached a maximum in 8 hr. Further incubation led to no further increase in the degree of lysis. The reaching of a

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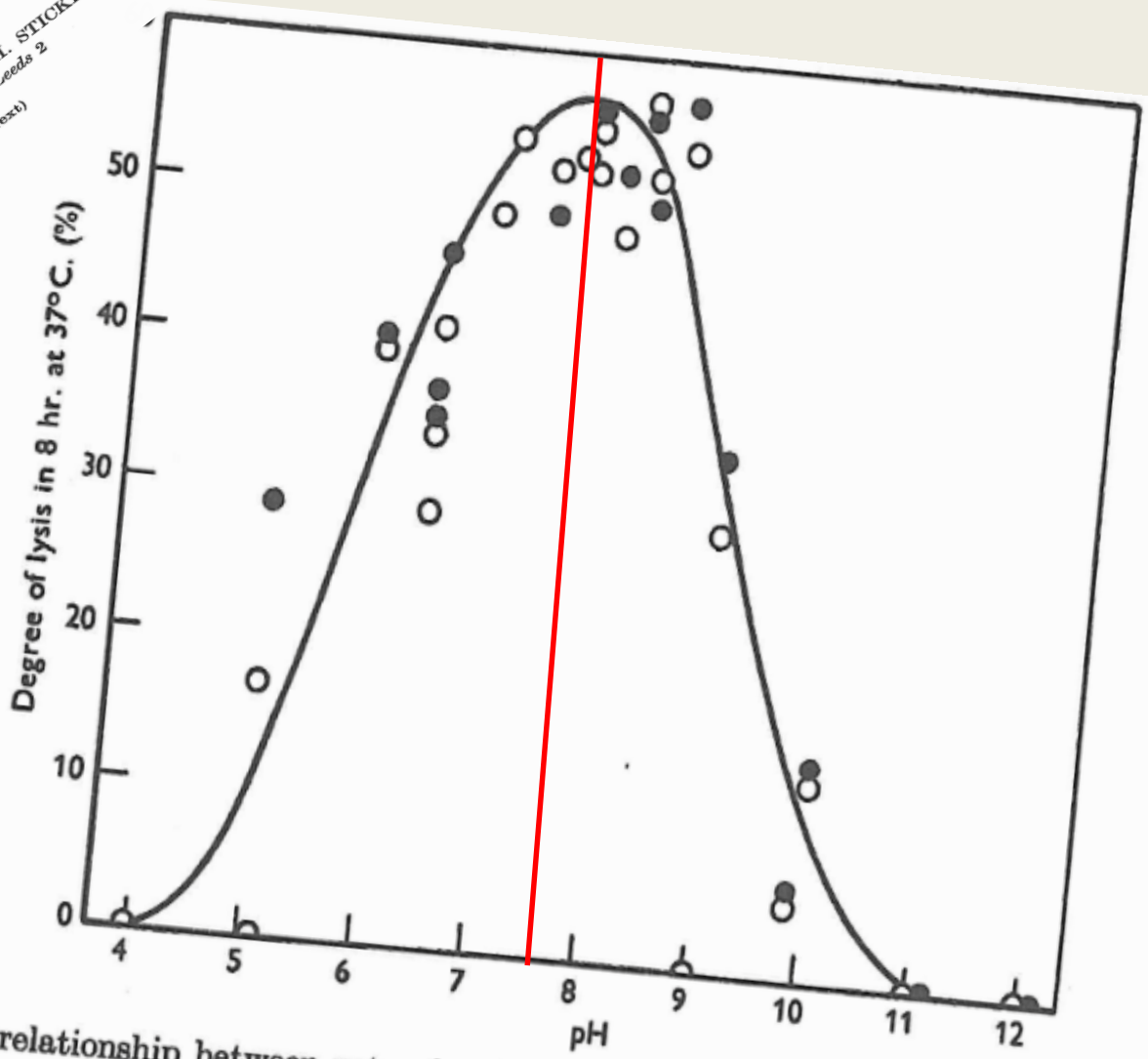

Fig. 3. The relationship between rate of lysis by glycine at 37° C. and pH. Two strains of *Bact. coli* were used, strain 7 (hollow circles) and strain 8 (solid circles). The results of four experiments are combined in the figure.

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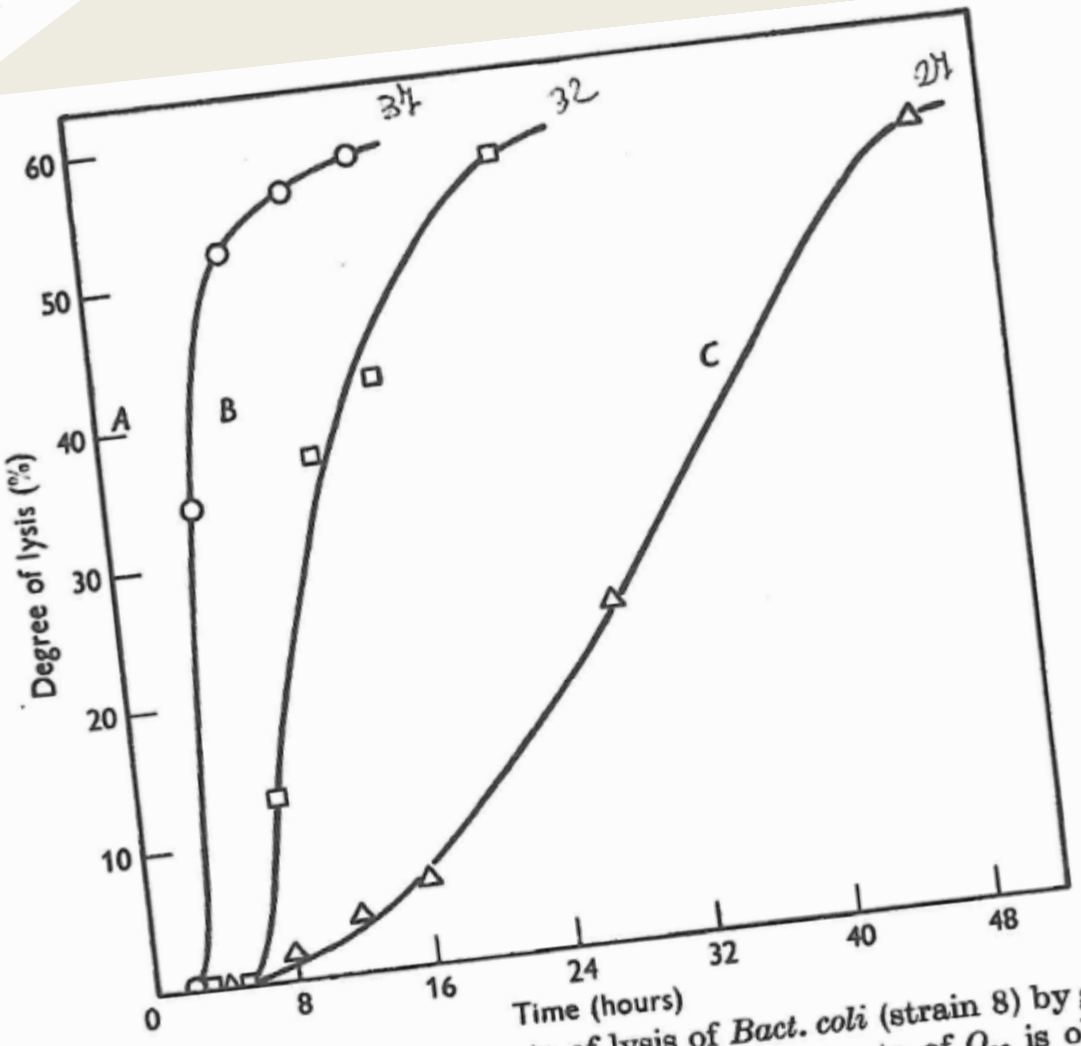

Fig. 4. The effect of temperature on the rate of lysis of *Bact. coli* (strain 8) by glycine (1·0M). ○——○, 37° C.; □——□, 32° C.; △——△, 27° C. The estimate of Q_{10} is obtained as the ratio AC/AB.

THE KINETICS OF THE LYSIS OF *BACTERIUM COLI* BY GLYCINE

By J. GORDON, R. A. HALL AND L. H. STICKLAND
From the School of Medicine, Leeds 2

(With 4 Figures in the Text)

The high temperature coefficient suggests that the process of lysis may be a chemical reaction. As Höber (1946) says: 'Many chemical reactions have Q_{10} values between 2 and 4, while a physical process . . . is apt to have a temperature coefficient in the neighbourhood of 1·2–1·3.'

SUMMARY

The lysis of *Bacterium coli* suspensions brought about by glycine shows the following characteristics:

(1) There is a latent period of 2 hr., followed by a rapid lysis reaching a maximum in about 8 hr.

(2) The extent of the lysis is independent of the dilution of the bacterial suspension over a wide range.

(3) The extent of the lysis increases with the glycine concentration up to 1·0 M, but is approaching a limit at this concentration.

(4) The lysis is negligible below pH 5 and above pH 10, and shows a maximum rate in the region of pH 6·5–8·5.

(5) The rate of lysis has a very high temperature coefficient (Q_{10} of the order of 5).

[Agr. Biol. Chem., Vol. 33, No. 11, p. 1577~1586, 1969]

Effects of Glycine and D-Amino Acids on Growth of Various Microorganisms

By Fumio Hishinuma, Kazuo Izaki and Hajime Takahashi

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Received May 7, 1969

Growth of various microorganisms in media containing high concentrations of glycine or D-amino acids was examined. Susceptibilities to glycine or D-amino acids differed among microorganisms, and the differences in susceptibility have no direct relation with Gram staining, morphological forms, and aerobic or anaerobic nature of the organisms. Certain glycine-resistant bacteria tested, which included *Bacillus cereus*, *Staphylococcus aureus* and *Serratia marcescens*, exhibited relatively high oxidative activities towards glycine. The inhibition of the growth of *Escherichia coli* by either glycine or D-amino acids, which included D-threonine, D-alanine and D-lysine, was reversed by L-alanine, partialy by L-serine, and not by L-lysine or L-threonine. These results suggest that the growth inhibition of microorganisms by D-amino acids was similar to that by glycine. The incorporation of L-alanine into *E. coli* cells which were preincubated with glycine was less than those of preincubated without glycine. Particularly, the incorporation into the cell wall fraction was most susceptible to glycine. An additive effect of penicillin and glycine was observed in the inhibition of cell wall biosynthesis as determined by the intracellular accumulation of N-acetylamino sugar compounds.

[Agr. Biol. Chem., Vol. 35, No. 13, p. 2050~2058, 1971]

Inhibition of L-Alanine Adding Enzyme by Glycine

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Received June 28, 1971

L-Alanine adding enzymes from *Bacillus subtilis* and *Bacillus cereus* which catalyzed L-alanine incorporation into UDPMurNAc were partially purified and the properties of the enzymes were examined. The enzyme from *B. subtilis* was markedly stimulated by reducing agents including 2-mercaptoethanol, dithiothreitol, glutathione and cysteine. Mn^{2+} and Mg^{2+} activated L-alanine adding activity and their optimal concentrations were 2 to 5 mM and 10 mM, respectively. The optimum pH was 9.5 and the *Km* for L-alanine was 1.8×10^{-4} M. L-Alanine adding reaction was strongly inhibited by *p*-chloromercuribenzoate and N-ethylmaleimide. Among glycine, L- and D-amino acids and glycine derivatives, glycine was the most effective inhibitor of the L-alanine adding reaction. The enzyme from *B. cereus* was more resistant to glycine than that from *B. subtilis*. Glycine was incorporated into UDPMurNAc in place of L-alanine, and the *Ki* for glycine was 4.2×10^{-3} M with the enzyme from *B. subtilis*. From these data, the growth inhibition of bacteria by glycine is discussed.

JOURNAL OF BACTERIOLOGY, Nov. 1973, p. 1029–1053

Vol. 116, No. 2
Printed in U.S.A.

Mode of Action of Glycine on the Biosynthesis of Peptidoglycan

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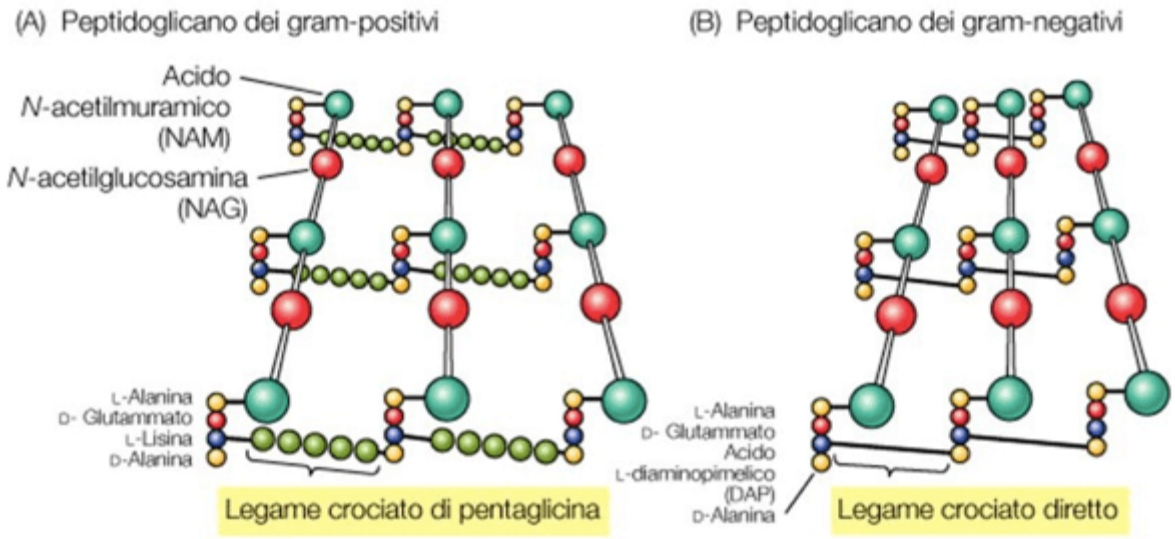
Received for publication 9 August 1973

The mechanism of glycine action in growth inhibition was studied on eight different species of bacteria of various genera representing the four most common peptidoglycan types. To inhibit the growth of the different organisms to 80%, glycine concentrations from 0.05 to 1.33 M had to be applied. The inhibited cells showed morphological aberrations. It has been demonstrated that glycine is incorporated into the nucleotide-activated peptidoglycan precursors. The amount of incorporated glycine was equivalent to the decrease in the amount of alanine. With one exception glycine is also incorporated into the peptidoglycan. Studies on the primary structure of both the peptidoglycan precursors and the corresponding peptidoglycan have revealed that glycine can replace L-alanine in position 1 and D-alanine residues in positions 4 and 5 of the peptide subunit. Replacement of L-alanine in position 1 of the peptide subunit together with an accumulation of uridine diphosphate-muramic acid (UDP-MurNAc), indicating an inhibition of the UDP-MurNAc:L-Ala ligase, has been found in three bacteria (*Staphylococcus aureus*, *Lactobacillus cellobiosus* and *L. plantarum*). However, discrimination against precursors with glycine in position 1 in peptidoglycan synthesis has been observed only in *S. aureus*. Replacement of D-alanine residues was most common. It occurred in the peptidoglycan with one exception in all strains studied. In *Corynebacterium* sp., *C. callunae*, *L. plantarum*, and *L. cellobiosus* most of the D-alanine replacing glycine occurs C-terminal in position 4, and in *C. insidiosum* and *S. aureus* glycine is found C-terminal in position 5. It is suggested that the modified peptidoglycan precursors are accumulated by being poor substrates for some of the enzymes involved in peptidoglycan synthesis. Two mechanisms leading to a more loosely cross-linked peptidoglycan and to morphological changes of the cells are considered. First, the accumulation of glycine-containing precursors may lead to a disrupture of the normal balance between peptidoglycan synthesis and controlled enzymatic hydrolysis during growth. Second, the modified glycine-containing precursors may be incorporated. Since these are poor substrates in the transpeptidation reaction, a high percentage of muropeptides remains uncross-linked. The second mechanism may be the more significant in most cases.


(A) Peptidoglicano dei gram-positivi
Acido
N-acetilmuramico
(NAM)
N-acetilglucosamina
(NAG)
L-Alanina
D- Glutammato
L-Lisina
D-Alanina
Legame crociato di pentaglicina
(B) Peptidoglicano dei gram-negativi
L-Alanina
D- Glutammato
Acido
L-diaminopimelico
(DAP)
D-Alanina
Legame crociato diretto

Review
Curr Pharm Biotechnol . 2024;25(13):1664-1692. doi: 10.2174/0113892010271172231108190233.

Potential of Flavonoids as Promising Phytotherapeutic Agents to Combat Multidrug-Resistant Infections

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PMID: 38031767
DOI: 10.2174/0113892010271172231108190233

Abstract

Background: Considering the limited number of current effective treatments, **Multidrug- Resistant (MDR)** illnesses have grown to be a serious concern to public health. It has become necessary to look for new antimicrobial drugs because of the emergence of resistance to numerous kinds of antibiotics. The use of **flavonoids is one phytotherapeutic strategy that has been researched as a potential remedy for this issue**. Secondary plant compounds called **flavonoids have been found to have an antibacterial effect against resistant microorganisms.**

Objective: This review seeks to give readers a glimpse into contemporary studies on flavonoids' potential to fight MDR infections.

Methods: A systematic search was conducted on electronic databases (PubMed, Scopus, and Google Scholar) using relevant keywords such as flavonoids, MDR infections, antimicrobial activity, and resistance microbes. Studies that investigated the antimicrobial activity of flavonoids against resistant microbes were included in this review.

Results: Most research found that flavonoids have antibacterial efficacy against resistant microorganisms, and some also showed that they have synergistic benefits with traditional antibiotics. The flavonoids **quercetin, kaempferol, apigenin, and luteolin** were the most often investigated ones. According to research, flavonoids affect microbial gene expression, inhibit microbial enzymes, and disrupt the integrity of microbial cell membranes. Additionally, a few studies have noted the flavonoids' low toxicity and safety.

Conclusion: For the treatment of infections that are resistant to many drugs, flavonoids constitute a promising class of phytotherapeutic agents. To develop flavonoid-based treatment methods for treating MDR illnesses and assess the potential of flavonoids as adjuvants to conventional antimicrobial drugs, more study is required.

Gli AMP furono scoperti nel 1939, quando il microbiologo René Dubos ha isolato da un ceppo di Bacillus del suolo, un agente antimicrobico, denominato gramicidina, che ha dimostrato di proteggere i topi dall'infezione da pneumococco (Van Epps, 2006). Successivamente sono stati scoperti diversi AMP sia del regno procariotico che

Attività antimicrobica di diversi peptidi antimicrobici (AMP) contro lo Staphylococcus aureus meticillino-resistente (MRSA).pdf

eucariotico (Boparai e Sharma, 2020), tra cui la tirocidina, prodotta dal batterio *Bacillus brevis*, con attività contro i batteri, e la purotionina, identificata nella pianta Triticum aestivum, attiva contro funghi e batteri (Ohtani et al., 1977). Il primo AMP di origine animale descritto è la defensina, che è stata isolata da leucociti di coniglio (Hirsch, 1956); successivamente la lattoferrina è stata identificata nel latte vaccino (Groves et al., 1965) ed è stato dimostrato che i lisosomi dei leucociti umani (Zeya e Spitznagel, 1966) e il tratto riproduttivo femminile umano contengono AMP a basso peso molecolare (Sharma et al., 2011). Ad oggi, sono stati scoperti, caratterizzati e annotati più di 3.000 AMP nel database AMP (APD3) (Huan et al., 2020), considerando che la sola pelle di rana è un serbatoio di oltre 300 AMP diversi (Boparai e Sharma, 2020).

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| Bacteriology | Research Article

Glycine restores the sensitivity to antibiotics in multidrug-resistant bacteria

Cesira Giordano,[1] Simona Barnini[1]

August 2024 Volume 12 Issue 8

Figura 2.
Curve di crescita di due ceppi di Klebsiella pneumoniae ATCC, 1706 e 1705, e di due isolati clinici appartenenti a ST512 (1084) e a ST307 (1129) in presenza di glicina a diverse concentrazioni.

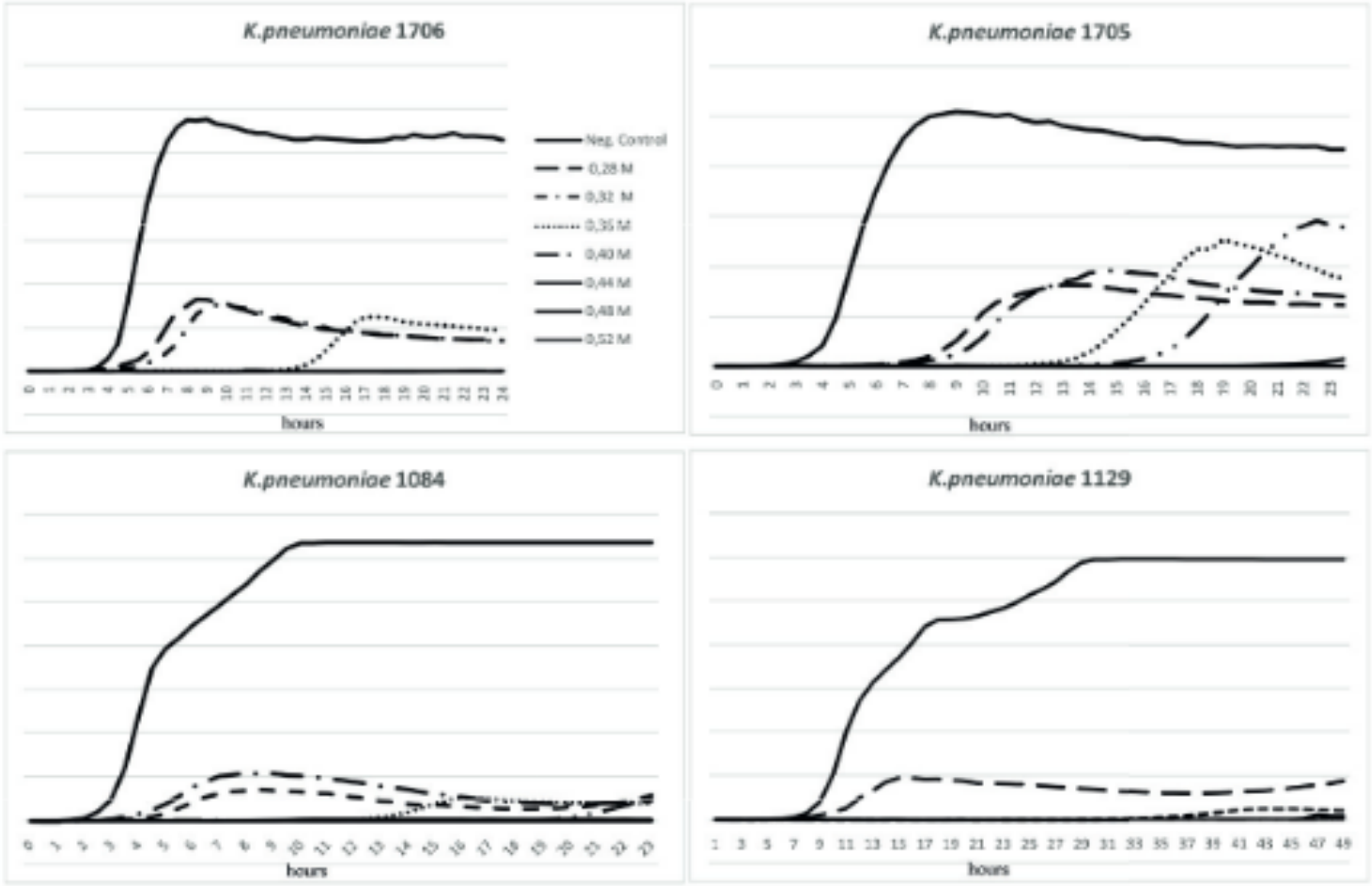

TABLE 2 Checkerboard results showing glycine and meropenem MICs and the effect of their combination[a]

Isolates	MIC				FiC	FiC	FiCi
	Meropenem (mg/L)	Glycine (M)	Mer + Gly (mg/L)	Gly + Mer (M)	Mer	Gly	
Klebsiella pneumoniae ATCC 1705	4	0·40	0·5	0·28	0·13	0·70	0·83
Klebsiella pneumoniae ATCC 1706	0·5	0·44	0·12	0·28	0·24	0·46	0·88
Klebsiella pneumoniae KPC 1084	64	0·44	4	0·40	0·06	0·90	0·97
Klebsiella pneumoniae KPC 1091	64	0·44	2	0·40	0·03	0·90	0·93
Klebsiella pneumoniae KPC 1043	64	0·40	2	0·32	0·03	0·80	0·83
Klebsiella pneumoniae KPC1059	64	0·40	4	0·32	0·06	0·80	0·86
Klebsiella pneumoniae KPC1076	64	0·44	0·5	0·36	0·01	0·82	0·83
Klebsiella pneumoniae KPC1079	64	0·44	2	0·36	0·03	0·82	0·85
Klebsiella pneumoniae KPC1123	64	0·40	4	0·36	0·06	0·90	0·96
Klebsiella pneumoniae KPC1129	16	0·36	2	0·28	0·13	0·78	0·91
Klebsiella pneumoniae KPC1145	64	0·40	4	0·32	0·06	0·80	0·86
Klebsiella pneumoniae KPC1206	32	0·40	2	0·28	0·06	0·70	0·76
Klebsiella pneumoniae NDM 1	8	0·44	1	0·28	0·13	0·64	0·76
Klebsiella pneumoniae NDM 2	64	0·44	4	0·36	0·06	0·82	0·88
Klebsiella pneumoniae NDM 7	64	0·40	1	0·28	0·02	0·70	0·72
Klebsiella pneumoniae NDM 8	8	0·44	0·5	0·25	0·06	0·57	0·63
Klebsiella pneumoniae NDM 9	64	0·40	0·5	0·32	0·01	0·80	0·81
Klebsiella pneumoniae NDM 10	64	0·44	0·25	0·36	0·00	0·82	0·82
Klebsiella pneumoniae NDM 11	16	0·40	0·5	0·28	0·03	0·70	0·73
Klebsiella pneumoniae NDM 12	64	0·44	0·25	0·32	0·00	0·73	0·73
Klebsiella pneumoniae NDM 14	64	0·44	1	0·28	0·02	0·64	0·65
Klebsiella pneumoniae NDM 15	64	0·44	0·5	0·32	0·01	0·73	0·74
Klebsiella pneumoniae NDM 16	32	0·40	2	0·28	0·06	0·70	0·76
Klebsiella pneumoniae NDM 17	16	0·40	1	0·28	0·06	0·70	0·76
Klebsiella pneumoniae NDM 18	8	0·40	0·5	0·28	0·06	0·70	0·76

TABLE 3 Checkerboard results showing glycine and colistin MICs and the effect of their combination[a]

Isolates	MIC				FiC	FiC	FiCi
	COL (mg/L)	Glycine (M)	COL + Gly (mg/L)	Gly +COL (M)	COL	Gly	
Klebsiella pneumoniae COLR 1	8	0.52	1	0.4	0.13	0.77	0.89
Klebsiella pneumoniae COLR 2	8	0.52	1	0.4	0.13	0.77	0.89
Klebsiella pneumoniae COLR 3	32	0.48	0.5	0.36	0.02	0.75	0.77
Klebsiella pneumoniae COLR 4	32	0.48	0.5	0.36	0.02	0.75	0.77
Acinetobacter baumannii COLR 1	4	0.4	0.25	0.28	0.06	0.7	0.76
Acinetobacter baumannii COLR 2	64	0.4	0.25	0.36	0	0.9	0.9

[a]COL, colistin; R, resistant; Gly, glycine; FiC, fractional inhibitory concentration; i, index.

TABLE 4 Checkerboard results showing glycine and cefidrocol MICs and the effect of their combination[a]

Isolates	MIC				FiC	FiC	FiCi
	CFD (mg/L)	Glycine (M)	CFD + Gly (mg/L)	Gly +CFD (M)	CFD	Gly	
Klebsiella pneumoniae CFDR 1	128	0.4	1	0.28	0.01	0.7	0.71
Klebsiella pneumoniae CFDR 2	128	0.44	1	0.32	0.01	0.73	0.74
Klebsiella pneumoniae CFDR 3	64	0.4	0.5	0.28	0.01	0.7	0.71
Klebsiella pneumoniae CFDR 4	64	0.44	1	0.28	0.02	0.64	0.65
Klebsiella pneumoniae CFDR 5	64	0.44	1	0.28	0.02	0.64	0.65
Acinetobacter baumannii CFDR 6	128	0.44	4	0.32	0.03	0.73	0.76
Acinetobacter baumannii CFDR 7	64	0.44	8	0.32	0.13	0.73	0.85
Acinetobacter baumannii CFDR 8	64	0.4	4	0.32	0.06	0.8	0.86
Acinetobacter baumannii CFDR 9	8	0.44	2	0.32	0.25	0.73	0.98
Acinetobacter baumannii CFDR 10	64	0.4	8	0.28	0.13	0.7	0.83

[a]CFD, cefiderocol; R, resistant; Gly, glycine; FiC, fractional inhibitory concentration; i, index.

Figura 3.
Un esempio di ripristino fenotipico della suscettibilità ad antibiotici beta-lattamici, in presenza di glicina, da parte di un ceppo nosocomiale di K. pneumoniae

Klebsiella pneumoniae, isolato clinico, ST512, KPC3, resistente a colistina

antibiotico	*MIC mg/L*	*SIR*
amikacina	>16	
amoxicillina/clavulanato	>8/2	R
ampicillina/sulbactam	32/16	R
cefepime	2	S
cefotaxime	>4	R
ceftazidime	64	R
ciprofloxacina	>2	R
colistina	>8	R
doripenem	>8	R
ertapenem	>1	R
fosfomicina	16	
gentamicina	2	
imipenem	8	R
meropenem	64	R
piperacillina/tazobactam	>128/4	R
tigeciclina	0.12	
trimetoprim-sulfametossazolo	>76/4	R

antibiotico + glicina	*MIC mg/L*	*SIR*
amikacina	**8**	
amoxicillina/clavulanato	>8/2	R
ampicillina/sulbactam	32/16	R
cefepime	<1	S
cefotaxime	**0.06**	**S**
ceftazidime	**1**	**S**
ciprofloxacina	>2	R
colistina	**<0.5**	**S**
doripenem	**<0.5**	**S**
ertapenem	**<1**	**S**
fosfomicina	16	
gentamicina	2	
imipenem	<1	R
meropenem	**0.12**	**S**
piperacillina/tazobactam	**<2**	**S**
tigeciclina	0.12	
trimetoprim-sulfametossazolo	32/2	S

Review Article

Multifarious Beneficial Effect of Nonessential Amino Acid, Glycine: A Review

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Received 3 November 2016; Revised 7 February 2017; Accepted 7 February 2017; Published 1 March 2017

Academic Editor: Musthafa Mohamed Essa

Glycine is most important and simple, nonessential amino acid in humans, animals, and many mammals. Generally, glycine is synthesized from choline, serine, hydroxyproline, and threonine through interorgan metabolism in which kidneys and liver are the primarily involved. Generally in common feeding conditions, glycine is not sufficiently synthesized in humans, animals, and birds. Glycine acts as precursor for several key metabolites of low molecular weight such as creatine, glutathione, haem, purines, and porphyrins. Glycine is very effective in improving the health and supports the growth and well-being of humans and animals. There are overwhelming reports supporting the role of supplementary glycine in prevention of many diseases and disorders including cancer. Dietary supplementation of proper dose of glycine is effectual in treating metabolic disorders in patients with cardiovascular diseases, several inflammatory diseases, obesity, cancers, and diabetes. Glycine also has the property to enhance the quality of sleep and neurological functions. In this review we will focus on the metabolism of glycine in humans and animals and the recent findings and advances about the beneficial effects and protection of glycine in different disease states.