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Antibacterial action of dipeptides containing an inhibitor of glucosamine-6-phosphate isomerase.

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Abstract

Several dipeptides, containing the N3-(4-methoxyfumaroyl)-L-2,3-diaminopropanoic acid (FMDP) moiety linked to protein and non-protein amino acids, exhibited a strong growth-inhibitory and bactericidal effect against Bacillus subtilis. FMDP-dipeptides were efficiently transported into bacterial cells by a di-tripeptide permease and subsequently cleaved by intracellular Mn2+/Co2+-dependent peptidases. Cleavage rates [0.1-5.6 micromol min-1 (mg protein)-1] were about two orders of magnitude lower than transport rates [40-200 micromol min-1 (mg dry wt)-1]. The released FMDP inactivated glucosamine-6-phosphate (GlcN-6-P) isomerase, an enzyme catalysing the first committed step in a biosynthetic pathway leading to amino sugar-nucleotide precursors of bacterial peptidoglycan. Inhibition of GlcN-6-P isomerase precluded peptidoglycan biosynthesis and resulted in a strong bacteriolytic effect. Results of the studies on consequences of GlcN-6-P isomerase inhibition upon the action of FMDP-dipeptides provided evidence demonstrating that the lack of endogenous GlcN-6-P could be a reason for the triggering of bacterial autolysis. Peptides containing the inhibitors of GlcN-6-P isomerase are one of the very few antimicrobial agents known that exhibit both bactericidal and fungicidal effects.

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