Award Lecture

Summary

Fattiviracins, Antiviral Antibiotics Produced by an Actinomycete

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(Received Sep. 30, 2004)

In 1995, we discovered new antihepetic antibiotics, called fattiviracins. The producing organism was classified as a strain belonging to *Streptomyces microflavus*. The strain produced at least 13 fattiviracin derivatives (FV-1 to FV-13). Fattiviracins were obtained as a amorphous powder, and their molecular weights are in the range of 1400 to 1500. They are readily soluble in water, methanol, pyridine, and DMSO, but insoluble in other organic solvents. Fattiviracins have macrocyclic diesters formed by the binding of two trihydroxy fatty acids and two D-gulose residues in the molecule, and they can be divided into five families according to the length of the fatty acid moiety.

Fattiviracins have potent activity against enveloped DNA viruses such as the herpes family, HSV-1, and VZV and enveloped RNA viruses such as influenza A and B viruses, and three strains of HIV-1, with EC_{50} values on the order of a few micrograms per milliliter. The biosynthetic pathway of fattiviracins was made clear.

We demonstrate that the *Streptomyces microflavus* strain No. 2445 that acquired resistance for bacitracin (BC) exhibits significant quantitative and qualitative alteration in the production of fattiviracins. The MIC of the wild strain to BC was 10 μ g/ml. After 5 to 6 transfers onto MGA agar plates containing the raised concentrations of BC, BC-resis-

tant strains (BCR) designated as 40-BCR, 120-BCR and 350-BCR grown on the plates containing 40, 120 and 350 μ g/ml of BC, respectively, were obtained.

Comparison of the wild strain and 40-BCR with respect to fattiviracin production was carried out. 40-BCR produced 2.1 times more fattiviracins than the wild strain. To investigate the fattiviracin components produced by the respective strain, the 6-day cultures were partially purified and fattiviracin components in the crude sample were analyzed with an analytical HPLC. As a result, by BC-resistant strain, enhanced and astringent production of fattiviracins was achieved. Fattiviracin FV-13, which has the longest fatty acid chains in the molecule, was dramatically enhanced by a C_{55} -isoprenyl phosphate metabolism.

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Details on this study were published in Actinomycetologica 17, 57–66 (2003).

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