

4-Methylpseudoproline analogues of cyclolinopeptide A: synthesis, structural analysis and evaluation of their suppressive effects in selected immunological assays.

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Streszczenie

The synthesis of new analogues of cyclolinopeptide A (CLA) and their linear precursors modified with (*R*)- and (*S*)-4-methylpseudoproline in the Pro³-Pro⁴ fragment are presented. The peptides were tested in comparison with cyclosporine A (CsA) in concanavalin A (Con A) and pokeweed mitogen (PWM)-induced mouse splenocyte proliferation and in secondary humoral immune response *in vitro* to sheep erythrocytes (SRBC). Their effects on expression of selected signaling molecules in the Jurkat T cell line were also determined. In addition, the structural features of the peptides, applying nuclear magnetic resonance and circular dichroism, were analyzed.

The results showed that only peptides 7 and 8 modified with (*R*)-4-methylpseudoproline residue (c(Leu¹-Val²-(*R*)-(αMe)Ser(ΨPro)³-Pro⁴-Phe⁵-Phe⁶-Leu⁷-Ile⁸-Ile⁹) and c(Leu¹-Val²-Pro³-(*R*)-(αMe)Ser(ΨPro)⁴-Phe⁵-Phe⁶-Leu⁷-Ile⁸-Ile⁹), respectively) strongly suppressed mitogen-induced splenocyte proliferation and the humoral immune response, with peptide 8 being more potent. Likewise, peptide 8 more strongly elevated expression of Fas, a proapoptotic signaling molecule in Jurkat cells. We postulate that the increased biological activity of peptide 8, compared to the parent molecule and other studied peptides, resulted from its more flexible structure, found on the basis of both CD and NMR studies. CD and NMR spectra showed that replacement of Pro³ by (*R*)-(αMe)Ser(-Pro) caused much greater conformational changes than the same replacement of the Pro⁴ residue. Such a modification could lead to increased conformational freedom of peptide 8, resulting in a greater ability to adopt a more compact structure, better suited to its putative receptor. In conclusion, peptide 8 is a potent immune suppressor which may find application in controlling immune disorders.

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