VASOCONSTRICTOR EFFECTS OF CONFORMATIONAL RESTRICTED GALANIN FRAGMENTS

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Galanin (Gal) is a 29-amino-acid neuropeptide which was originally isolated from the porcine gut (GWTLNSAKGLLGPHAIDNHRSFHDKYGLA-NH_2) [Tatemoto, K. et al. FEBS Lett. 164, 124, 1983]. Gal has been involved in multiple physiological functions including central cardio-vascular control, feeding, insulin release, lactation, gut contractility, and growth and has effects on central functions, learning, and memory and in rodent models of depression. Our goal is to investigate the SAR of a series of Gal-related fragments of restricted conformation by the insertion of different sizes and chirality of lactama bridges. Peptides were synthesized by SPPS, purified by HPLC, and characterized by LC/MS. Biological activities were determined in jejunum and colon of Wistar rats of both sexes. Conformational studies were performed by CD in different environments. Gal_{1-16}, Cyclo(4/8)[Asp^4, Lys^8]-Gal_{1-16} were equipotent to Gal. Cyclo(4/8)[Glu^4, Lys^8]-Gal_{1-16} and Gal_{1-15} showed relative potency of 50% in comparison to Gal. Cyclo(4/8)-[Asp^4, Dap^8]-Gal_{1-16} e Cyclo(4/8)-[Asp^4,Orn^8]-Gal_{1-16} were practically inactive. Cyclo(4/8)[D-Asp^4, Lys^8]-Gal_{1-16} showed to be more potent than the standard peptide. We also have scanned the whole gal sequence with an i-(i+4) bridge consisting of the DAsp-X-Y-Z-Lys scaffold. Most analogues were less potent than Gal1-16 with exception of analogues with lactam bridges in position 3-7, 4-8 and 5-9 that were equipotent. Interestingly its CD spectrum was very similar than the one observed of Gal in 90% TFE. From our results we concluded that the conformational restriction was important to the maintenance of the biological activity and that the best size and chirality for the cyclo was obtained by the incorporation of the D-Asp and Lys residues as bridge-heads component in the sequence region from 3 to 9.

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