Study of the interaction of 1,4-dihydropyridine derivatives with glucocorticoid hormone receptors from the rat liver

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Abstract:
Seventeen derivatives of 1,4-dihydropyridine (DHP) series were tested in vitro for their ability to inhibit [1,2,4⁻³H]-dexamethasone binding to glucocorticoid receptor from the rat liver cytosol. Depending on structural features and inhibiting activities, the compounds can be divided into three groups. The first group (nifedipine, foridone, J-6-163, OSI-4164 and OSI-7724) had the highest activity: they inhibited specific ligand-receptor binding by 70–80% at concentrations of 10⁻⁶ M and 10⁻⁷ M, with apparent IC₅₀ values of 1.5–6.0 µM. The second group (cerebrocrast, diethone, OSI-1211 and OSI-7265) was active at concentration of 10⁻⁴ M, and their IC₅₀ values were 23–45 µM; compound OSI-5003 was almost inactive. Both groups are compounds with scarce water solubility, more or less lipophilic. The third group of compounds comprises ionogenic compounds (organic cations or anions with corresponding inorganic counterions): most of them are water-soluble (glutapyrone, carbatone, gammapyrone, OSI-2780, OSI-1580, OSI-2140) or liposome-forming (A-74). They lack the above-mentioned activity. Among the first two groups, compounds possessing more bulky substituents in positions 3 and 5 are less active. The aromatic ring in the position 4 is essential for the optimal activity. It seems that there is a bell-shaped dependence of activity upon lipophilicity. In general, the compounds of the first group are strong Ca-antagonists, while the second group includes moderate Ca-antagonists, but each group comprises also compounds which lack Ca antagonistic activity. All compounds of the third group lack Ca antagonistic properties.

Key words:
1,4-dihydropyridines, glucocorticoid receptor