2-H- and 2-acyl-9-{o-[4-(2-methoxyphenyl)piperazinyl]-alkyl}-1,2,3,4-tetrahydro-\(\beta\)-carbolines as ligands of 5-HT\(_{1A}\) and 5-HT\(_{2A}\) receptors

Jan Boksa*##, Maria J. Mokrosz†, Sijka Charakchieva-Minol§, Ewa Tatarczyńska¶, Aleksandra Klodzińskaª, Anna Wesołowskaª, Stanisław Misztalº.

*Department of Medicinal Chemistry, †Department of New Drug Research, Institute of Pharmacology, Polish Academy of Sciences, Smeńa 12, PL-31-343 Kraków, Poland

Three series of new unsubstituted or 2-acyl 1,2,3,4-tetrahydro-\(\beta\)-carbolines (THBC), connected to 1-(o-methoxyphenyl)piperazine by 2-, 3- or 4-membered alkylene spacer (3, 4 or 5, respectively) in position 9, were synthesized and their 5-HT\(_{1A}\)/5-HT\(_{2A}\) receptor affinities and functional in vivo activities were investigated. Radioligand binding studies showed that unsubstituted (a) and acyl (b–f) derivatives with prop-1,3ylene (4) and particularly with but-1,4ylene (5) spacer had a high 5-HT\(_{1A}\) receptor affinity (K\(_{i}\) = 30–110 nM), whereas the 5-HT\(_{1A}\) affinity of derivatives with ethylene spacer (3) was low. All those compounds (except 5c, K\(_{i}\) = 44 nM) did not distinctly bind to 5-HT\(_{2A}\) receptors. The obtained results indicated that the length of an alkylene chain was a crucial parameter for determining 5-HT\(_{1A}\) receptor affinities of the tested compounds, while acyl substituents in position 2 of THBC were not important for their 5-HT\(_{1A}\)/5-HT\(_{2A}\) activities. It was also demonstrated that the few selected compounds (4d, 5a–c and 5e) with the highest affinity (K\(_{i}\) up to 50 nM) for 5-HT\(_{1A}\) receptors, administered at doses of 10–20 mg/kg, behaved like antagonists of postsynaptic 5-HT\(_{1A}\) receptors, as they reduced the 8-OH-DPAT (5-HT\(_{1A}\) agonist)-induced lower lip retraction and behavioral syndrome in rats. Moreover, 4d seemed to be an agonist of presynaptic 5-HT\(_{1A}\) receptors, since the hypothermia induced by its administration was attenuated by WAY 100635 (5-HT\(_{1A}\) antagonist). Compound 5c, 5-HT\(_{2A}\) receptor ligand, demonstrated an antagonistic activity, as it inhibited the (+)-DOI (5-HT\(_{2A}\) agonist)-induced head twitches in mice.

The obtained results of in vivo studies suggest that introduction of different acyl substituents in position 2 of THBC with propylene or butylene spacer between tricyclic and arylpiperazine moiety is insignificant for the postsynaptic 5-HT\(_{1A}\) receptor activity of the compounds tested in vivo. On the other hand, only compound 5e with an acryloyl group and a butylene chain behaved like a 5-HT\(_{1A}\)/5-HT\(_{2A}\) antagonist.

Key words: 1,2,3,4-tetrahydro-\(\beta\)-carbolines, 2-methoxyphenylpiperazine, 5-HT\(_{1A}\) ligands, 5-HT\(_{1A}\) antagonists

##... correspondence