PHARMACOLOGICAL CHARACTERIZATION OF A NEW NON-IMIDAZOLE HISTAMINE H_3 ANTAGONIST

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Experimental evidence suggests that histamine H_3 antagonists are potential therapeutic agents for several CNS disorders such as cognitive dysfunctions, narcolepsy, epilepsy and obesity. Thioperamide, the prototypic imidazole derivative originally defined as highly selective and potent antagonist at rat and guinea-pig histamine H_3 receptors, proved to possess moderate affinity for both human H_3 and H_4 receptors (1) and to display pharmacokinetics liabilities, such as cytochrome P450 inhibition, leading to possible drug-drug interactions, and poor access to CNS. In order to overcome these drawbacks, the attention has turned towards the development of histamine H_3 antagonists lacking the imidazole nucleus. Previous studies, performed by our research group, have revealed the interesting binding properties of a new dibasic non-imidazole derivative, M57, to rat and human histamine H_3 receptors (pK_i=8.92 and pK_i=9.47 respectively) (2). Therefore, the aim of the present work is to gain a deeper insight into the pharmacological profile of M57, by evaluating its inhibitory potency towards guinea-pig and human H_3 receptors, its selectivity towards other (H_1, H_2, H_4) histamine and non-histamine receptors (α_2, μ and $5HT_3$ enteric guinea-pig receptors) and its ability to penetrate into CNS. In functional in vitro tests M57 demonstrated an antagonistic potency consistent with its binding affinity values (pK_B=8.58 and pK_B=8.77 towards guinea-pig and human H_3 receptors respectively), together with a favourable receptor selectivity profile. Besides, when tested in an ex-vivo binding assay considering the specific displacement of [^{3}H]Ralphamethylhistamine from cortical H_3 sites of rats pretreated with the compound under study, M57 revealed an easy access to CNS with a higher ex-vivo potency than thioperamide (ED_{50}=0.63 vs ED_{50}=2.04 mg/kg i.p. one hour after administration). Thus, M57 appears as a selective non-imidazole antagonist endowed with high potency towards both rodent and human histamine H_3 receptors and favourable drug-like properties.

(1) Leurs R., Bakker A., Timmerman H. and de Esch I.J.P. (2005) Nature Reviews 4: 107-120
(2) Morini M., Comini M., Rivara M., Rivara S., Lorenzi S., Bordi F., Mor M., Flammini L., Bertoni S., Ballabeni V., Barocelli E. and Plazzi P.V. (2006) Bioorg. Med. Chem. Letters 16: 4063-4067.