CNS ACCESS OF SELECTED H_3 ANTAGONISTS

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Over the past decade, it has become well established that in the brain the H_3 type of histamine receptor has a pre-synaptic auto and hetero receptor inhibitory role which regulates release and synthesis of histamine and other neurotransmitters. The H_3 receptor subtype seems to mediate histamine regulatory activity on physiological functions such as sleep-wakefulness cycle, feeding and drinking behaviour, cognition and memory processes. Recent studies suggest that H_3 antagonists could be useful in the treatment of various central disorders probably associated with low levels of histamine (e.g. attention/learning disabilities, epilepsy, narcolepsy, obesity) (1). Since CNS is the therapeutic target of these drugs, the ability to penetrate efficiently the BBB is a fundamental requirement for their potential clinical application.

The aim of the present work is to evaluate CNS access of six new imidazole H_3 antagonists (I-VI), endowed with moderate to high H_3 affinity, and of the prototype H_3 antagonist Thioperamide.

The study started using ex-vivo binding technique in female rats to evaluate ex-vivo potencies (ED_{50}) of tested drugs, administered intraperitoneally (i.p.) 1 h before the binding assay, in the displacement of [^{3}H]R-a-methylhistamine (0,5nM) from cerebral cortical membranes. This index, compared with pKi values of H_3 affinity, obtained from in vitro binding data in rat cerebral cortex, allowed us to establish the level of central penetration from a binding point of view. Some compounds demonstrated poor (compound V and compound II), comparable (compound III), or improved (compound IV) brain penetration with respect to Thioperamide.

In the following phase of this project we tried to investigate CNS access from a functional point of view, considering that histamine intracerebroventricular (i.c.v.) administration produced an arousal effect on Pentobarbital induced hypnosis in rats (2). Indeed the capacity of the compounds to modify narcosis duration after peripheral (i.p.) and central (i.c.v.) administration was evaluated. Except compound V and compound II, Thioperamide and the other H_3-blockers i.p. injected significantly prolonged Pentobarbital induced narcosis in a non-H_3 mediated way. When i.c.v. given at doses 20-fold lower than those peripherally effective, Thioperamide and compound IV prolonged Pentobarbital induced hypnosis as a conseguence of a possible central metabolic interference (3) or an increased GABA efflux (4). Only compound V has revealed the expected H_3-dependent arousal effect, being able to shorten significantly such narcosis.

In conclusion, this functional evidence points out the possible occurrence of metabolic interactions for Thioperamide with Pentobarbital and the interesting arousal properties of compound V.

At the present time further studies are in progress in order to evaluate the brain penetrating properties of two prodrugs, compound A and compound B, synthesised starting from the most interesting tested molecules, compound III and compound V respectively. Very preliminary data obtained from ex-vivo binding assays have not shown improved properties of brain access with respect to the parent compounds.

References

1. Leurs R., Blandina P., Tedford C., Timmerman H. *Therapeutic potential of histamine H_3 agonists and antagonists.* TiPS 19: 177-183, 1998.

2. Kalivas P.W. *Histamine-induced arousal in the conscious and in pentobarbital-pretreated rat.* J. Pharmacol. Exp. Ther. 222: 37-42, 1982.

3. Alves-Rodrigues A., Leurs R., Wu T.S., Prell G.D., Foged C., Timmerman H. [^{3}H] *Thioperamide as a radioligand for the histamine H_3-receptor in rat cerebral cortex.* Br. J. Pharmacol. 118: 2045-52, 1996.

4. Yamamoto Y, Mochizuki T., Okakura-Mochizuki K, Uno A., Yamatodani A. *Thioperamide, a histamine H_3 receptor antagonist, increases GABA release from the rat hypothalamus.* Meth. Find. Exp. Clin. Pharmacol. 19: 289-98, 1997.
