MOLECULAR BIOLOGY AND PHARMACOLOGY OF HISTAMINE RECEPTOR SUBTYPES

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Histamine is a neurotransmitter synthesized in a restricted population of neurons located in the tuberomammillary nucleus of the posterior hypothalamus and projecting diffusely to most cerebral areas. Histaminergic neurons might be involved in the control of sleep/wakefulness, hormonal secretions and affective functions.

Three histamine receptor subtypes, i.e. the H_1, H_2 and H_3 receptor, have been so far identified and localized in brain using biochemical, pharmacological and radioligand binding approaches (reviewed in Schwartz et al. (1)).

Whereas H_3 receptors are essentially defined pharmacologically, both H_1 and H_2 receptor proteins were previously defined biochemically and heterogeneity of these two subclasses of histamine receptors has been suggested (reviewed in Ruat et al. (2)). An affinity matrix for purification of the histamine H_1 receptor has been recently designed (3). However, using molecular biology approaches, their genes were recently cloned in several animal species. Both are intronless genes belonging to the superfamily of G protein-linked receptors with seven transmembrane domains.

The H_1 receptor is a target for several antidepressant and antipsychotic drugs displaying sedative properties in humans. The bovine gene encodes a 491 amino acid protein with a deduced molecular mass of 56 kDa (4) and we have recently cloned a homologous gene in the guinea pig, the two proteins displaying ~90% homology (Ruat, Traiffort, Leurs, Arrang, Tardivel-Lacombe, Diaz and Schwartz, in preparation). Northern blot analysis reveals a single transcript of 3.5 kb for the H_1 receptor gene in various guinea pig tissues. In the brain, this transcript is highly expressed in hippocampus, brainstem and to a lesser extent in cerebral cortex. Among peripheral tissues, the lung, the heart and the ileum were highly detected. In comparison (^{125}I)iodoazidophenpyramine, a specific photoaffinity probe, identified 56 kDa and 68 kDa peptides as the major H_1 receptor proteins in guinea pig brain (5) and heart (6) respectively.

The H_2 receptor, a possible target for antidepressant, corresponds to a 359 amino acid protein in dog (7) and man (8) and a 358 amino acid protein in rat with a deduced molecular weight of 40 kDa (9). In comparison a 59 kDa size was revealed by SDS-PAGE analysis of the photolabelled H_2 receptor in brain (10) using (^{125}I)iodoazidopotentidine as the specific probe.

Northern blot and in situ hybridization studies performed on rat tissues reveal a single 6 kb transcript expressed highly in brainstem and, to a lower extent, in hypothalamus and hippocampus. When expressed in CHO cells the rat H_2

receptor was found to bind (^{125}I)iodoaminopotentidine, a selective H_2-receptor probe and typical H_2 receptor ligands with the expected potencies (11).

In addition, this H_2 receptor mediates not only the expected activation of cAMP but also a potent inhibition of arachidonic acid release which is independent of both cAMP and Ca^{2+} levels and which appears to be a **novel signalling pathway for histamine H_2 receptors** (11). Because constitutive H_1 receptors have been reported to stimulate arachidonic acid release, this novel mechanism may explain the opposing physiological responses elicited in many tissues by stimulation of H_1 and H_2 receptors.

The 30-40% overall homology of amino acid sequence between cloned H_1 and H_2 receptors appears in the same range as the homology between subtypes of other aminergic receptors. A major difference in the structural features of the H_1 and H_2 receptors, and that of catecholamine receptors, is the absence of two serine residues in the fifth transmembrane domain (TM5) which presumably form hydrogen bonds with catechol hydroxyl groups. Aspartate^{186} and threonine^{190} in TM5 of the canine H_2 receptor, supposed to interact with the imidazol ring of histamine (7), are not found in the H_1-receptor protein. Although this might explain the observed differences in structural demands for histaminergic agonists at the H_1 and H_2 receptors, involvement of these residues remains to be confirmed.

References

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