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Ligand-5-HT$_{1A}$ receptor interaction

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Abstract

In the present paper the general structure and pharmacophore of some 5-HT$_{1A}$ receptor ligands are described. For several compounds ($\sim$15) the intrinsic activity in lower lip retraction (postsynaptic, rat) and hypothermia (presynaptic, mice) tests was determined. For the identified functional presynaptic agonists and antagonists the influence on the brain serotonin level was examined. No direct correlation between the functional intrinsic activity and the influence on the level was observed. Molecular modelling revealed the possibility of the existence of different binding sites for different examined compounds. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: 5-HT$_{1A}$ receptor ligands; Pharmacophore model; Intrinsic activity

1. Introduction

Considering ligand–receptor interaction one usually takes into account two points: strength of the interaction (what we refer to as 'affinity') and type of an effect at the biochemical, electrophysiological and behavioural level triggered by the ligand (what we refer to as 'intrinsic activity'). To get an insight into the type of chemical forces involved in the interaction one either builds models of a specific pharmacophore or constructs models of a receptor protein and examine the binding forces. Interaction of a ligand with a receptor may result in receptor activation (agonists), blockade (antagonists) or inactivation (inverse agonists).

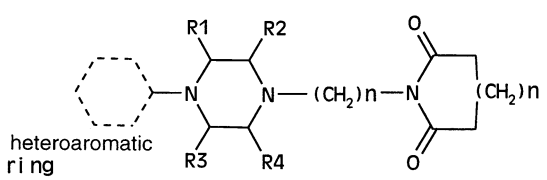

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Fig. 1. General structure of the prepared ligands.

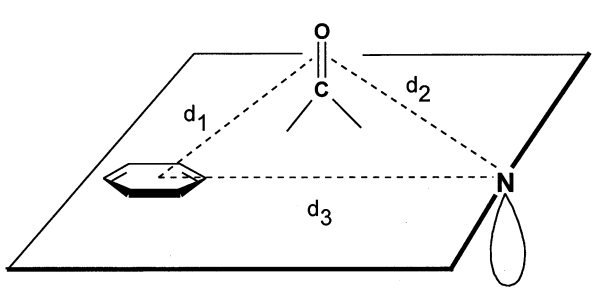

Fig. 2. Proposed pharmacophoric points for 5-HT$_{1A}$ receptor binding site.

2. Results and discussion

We synthesised several ligands of 5-HT$_{1A}$ receptor of general structure **1** (Fig. 1) possessing very high ($K_i \sim 10^{-9}$ M) to very low affinity [1–4].

Based on the models of Hibert et al. [5,6] and Mokrosz et al. [7] we proposed a three-point pharmacophore for the 5-HT$_{1A}$ receptor ligands (Fig. 2)[1] suggesting that conformational flexibility of a ligand may be a crucial factor influencing its affinity to the receptor [4].

Examination of the interactions between a series of ligands with a 3D model of the receptor protein revealed that for a series of ligands experimental affinity constants K_i might be reproduced from the corresponding ligand–receptor interaction energy [8].

For some of the prepared ligands ($\sim$15) pre- and postsynaptic intrinsic activity in hypothermia (mice) and lower lip retraction (rats) tests were determined [9].

[1] The distances d_1, d_2 and d_3 were defined on the basis of the relevant pharmacophoric distances in LSD, high affinity 5-HT$_{1A}$ receptor ligand.

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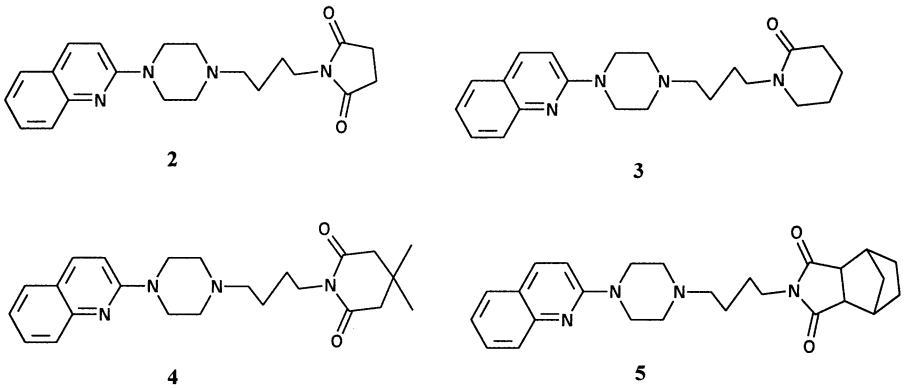

Fig. 3. Structures of exemplary compounds tested in behavioural functional tests.

It allowed us to identify presynaptic agonists (**2**, **3**) and antagonists (**4**, **5**) (Fig. 3). All the compounds were found to be functional postsynaptic antagonists. Since it known that such 5-HT_{1A} receptor agonists as buspirone, gepirone or ipsapirone may reduce serotonin synthesis/turnover (for a review see Ref. [10])[2] the influence of compounds **2**–**5** on the serotonin neurotransmission was examined. The systemic administration of compound **3** (functional presynaptic agonist), **4** (antagonist) and **5** (antagonist), lowered the serotonin level in the hippocampus and striatum of the rat brain while administration of compound **2** (agonist) did not influence the level. Examination of the influence of the compounds on serotonin turnover (as measured by the 5-hydroxyindoleacetic acid/5-hydroxytryptamine ratio) revealed that compounds **2** (functional presynaptic agonist), **4** (antagonist) and **5** (antagonist) (but not **3** (agonist)) significantly decreased the serotonin turnover in the striatum (but not in the hippocampus). Compound **3** elevated the serotonin turnover in hippocampus moderately.

Thus the influence exerted by the compounds on the brain serotonin neurotransmission did not prove any significant correlation between the intrinsic activity of the compounds at presynaptic 5-HT_{1A} receptors (as measured in the functional tests) and the neurotransmission. The results may be explained in terms of the observations made by Sprouse [12] and Manahan-Vaughan et al. [13], who found that the intrinsic activity of a compound might depend on a model in which the activity was tested[3]. It is also known that activation of a specific receptor may activate different signal transduction pathways. For instance 5-HT_{1A} receptors may modulate adenyl cyclase, phospholipase C and K^+ channel activities as well as Ca^{2+} level [14,15]. An important question is whether these different signal transduction pathways reflect multiple signalling mechanisms for a single receptor or reflect multiple receptor subtypes that cannot be differentiated with the available drugs. It is supposed that a single G-protein linked receptor can couple to different pathways. It is also anticipated that G-protein coupled receptors can adopt different conformations, which selectively and differentially couple them to a specific pathway [14,15]. Examination (by means of molecular modelling) of the interaction of the ligands of the general structure **1** revealed that the ligands may bind to different binding pockets at the 5-HT_{1A} receptor [1–4,8,17].

[2] The action is believed to be mediated through presynaptic somatodendric autoreceptors [11].

[3] It was, for instance, found that binospirone, examined in phase 1 clinical trials for an anxiety disorder, considered as a 5-HT_{1A} receptor antagonist [16], can exhibit different intrinsic activity in different functional tests. It inhibited the firing rate of dorsal raphé nuclei, thus indicating its agonistic activity at somatodendric autoreceptors [12]. On the other hand, it was observed that binospirone antagonised the reduction of the field excitatory postsynaptic potential produced by 8-OH-DPAT in the CA1 region of the rat hippocampus [13].

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