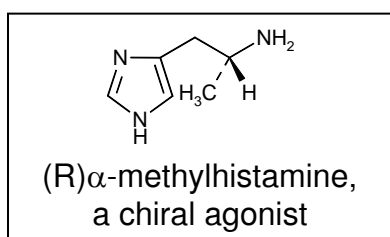


Design of highly potent and selective antagonists for histamine H₃ receptors

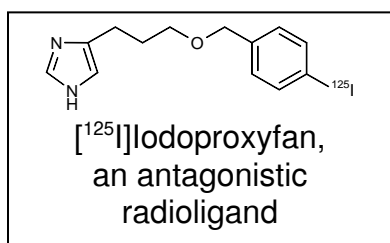
Holger Stark and Walter Schunack

It was in 1983 when Arrang, Garbarg and Schwartz observed that histamine inhibits its own synthesis and release by a negative feedback process and that these actions are mediated by a novel subclass of receptors (H₃). Since then we are interested in the development of highly potent and selective ligands for this receptor subtype. As a receptor subclass is ultimately defined by the use of highly selective agonists and antagonists and its function assessed by testing these agents in the living animal, we have designed at first (*R*)- α -methylhistamine, a chiral agonist, which displays high selectivity and potency at nanomolar concentrations *in vitro* [1].



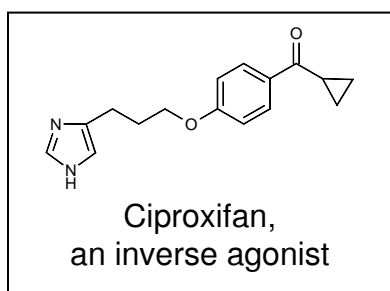
Labeling and autoradiographic visualization of H₃ receptors in the brain was first achieved by using (*R*)-[³H]- α -methylhistamine. However tritiated agonists do not allow a very sensitive detection of the H₃ receptor which is less abundant than other aminergic receptors.

receptors.



Therefore, we have designed [¹²⁵I]iodoproxyfan, a new antagonist to label and visualize cerebral H₃ receptors [2]. With this radioligand well contrasted autoradiographic pictures of the rat brain were obtained and the heterogenous distribution of H₃ receptors with high labeling of anterior cerebral cortex, ventral striatum and other limbic areas was confirmed.

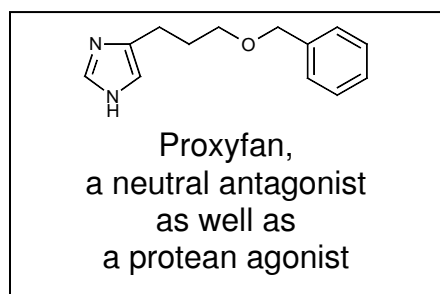
receptors with high labeling of anterior cerebral cortex, ventral striatum and other limbic areas was confirmed.



As H₃ receptor antagonists represent a class of agents with potentially interesting therapeutic applications, namely in psychiatry, sustained efforts have been devoted to design potent compounds. Ciproxifan is an orally bioavailable extremely potent and selective H₃-receptor antagonist with vigilance and attention-

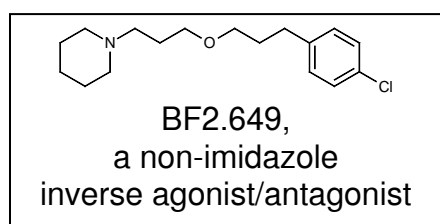
promoting effects [3]. It increased the waking state of cats and it reversed the H₃-receptor agonist induced enhancement of water consumption in rats.

The H₃ receptor displays high “constitutive activity”, that is, spontaneous activity in the absence of an agonist. Using the inverse agonist ciproxifan that abrogate this



activity and proxyfan, a neutral antagonist, that opposes both agonists and inverse agonists it could be demonstrated that constitutive activity of native H₃ receptors is present in rodent brain and that it controls histaminergic neuron activity *in vivo* [4].

However, proxyfan also acts as a protean agonist (after Proteus, the ancient Greek god who could change shape) at recombinant and native H₃ receptors known to display constitutive activity [5]. On neurochemical and behavioral responses in rodents and cats, proxyfan displays a spectrum of activity ranging from full agonism over partial agonism, neutral antagonism to partial inverse agonism and full inverse agonism.



Recently, the class of non-imidazole histamine H₃-receptor antagonists opened a broad and unexpectedly large variety of structural modifications maintaining affinity and, in most cases, even increasing selectivity. Different hybrid compounds or pharmacokinetically optimized compounds have been described. BF2.649 [6] is a novel, potent and selective non-imidazole inverse agonist at the recombinant human H₃ receptor. Its *in vitro* potency is about 10 times lower at the rodent than that at the human H₃ receptor. The preclinical data suggest that BF2.649 is a valuable drug candidate to be developed in wakefulness or memory deficits and other cognitive disorders.

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