Review

Histamine H₃ Receptor Antagonists Go to Clinics

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Within the recent years novel lead optimisations for histamine H₃ receptor antagonists made their way from bench to bedside. Structure–activity relationships, cross-affinities and side effects as well as pharmacokinetic profiling will be discussed on selected promising compound series. Due to diversity in potential therapeutic applications and in some cases a controversial debate, different indications will be highlighted with the potential and the problems of the test compounds, *e.g.* sleep–wake disorders, attention-deficient hyperactivity disorder, epilepsy, cognitive impairment, schizophrenia, obesity and neuropathic pain. First data published on clinical trials phase II (IIB) are presented showing proof of concept of H₃ receptor antagonists in narcolepsy and photo-induced epilepsy.

Key words histamine H₃; sleep disorder; cognition; schizophrenia; obesity; tiprolisant

INTRODUCTION

The biogenic amine histamine, 2-(1*H*-imidazol-4-yl)-ethanamine, is produced by decarboxylation of L-histidine and is implicated in a wide range of physiological and pathophysiological functions. It is metabolised by histamine *N*^ε-methyltransferase (HMT) and mono- or diaminoxidase. Histamine is mainly acting *via* four distinct metabotropic histamine receptor subtypes (H₁R–H₄R), which have meanwhile all been cloned. Whereas antagonists for H₁R and H₂R subtypes have been blockbusters in therapy of allergy and ulcer, respectively, antagonists for H₃R and H₄R subtypes are not on the market. The recently described H₄R seems to be involved in inflammatory and immunomodulatory processes. H₃Rs play a central role in neurotransmission of histamine and in control of many other neurotransmitters. Several antagonists are in preclinical and some in clinical stage of development.

PHARMACOLOGICAL BACKGROUND

Auto- and Heteroreceptor The H₃R was first described in 1983 as a presynaptic autoreceptor, which mediates synthesis of histamine and inhibition of its release from histaminergic neurons in slices of rat cerebral cortex.¹⁾ Localisation studies in rodents show a predominance in distinct regions of the central nervous system (CNS) as the H₃R is mainly located in *cerebral cortex*, *hippocampus*, *amygdala*, *nucleus accumbens*, *globus pallidus*, *striatum*, and *hypothalamus*^{2–5)} (Fig. 1). In addition, it is expressed in the peripheral nervous system, *e.g.* in gastrointestinal tract, airways and cardiovascular system.⁶⁾ Molecular aspects of the receptor,^{7–10)} structure–activity relationships (SAR) of ligands,^{11–19)} and pharmacology^{20–26)} have recently been resumed in many excellent reviews. This contribution focuses on the development of clinical candidates and the multifaceted potential indications targeted.

In mammalian brain histaminergic neurons originate in the tuberomammillary nucleus (TMN) spreading into above mentioned brain regions, where they control histamine levels by regulation of synthesis and liberation rates²⁷⁾ and modu-

late different neuronal systems.²⁸⁾ H₃R expression is not solely restricted to histaminergic neurons: due to its function as a heteroreceptor it can be found on colocalised neurons, and H₃R activation modulates the release of various important neurotransmitters, *i.e.* dopamine,^{29–33)} acetylcholine,^{34–37)} norepinephrine,^{38,39)} serotonin,^{40,41)} GABA,^{42–44)} glutamate,⁴⁵⁾ and substance P.^{46–48)} Therefore, histaminergic neurons and the cross-linkage between major neurotransmitter systems are involved in many (patho)physiological brain functions, including vigilance, memory processes, feeding behaviour and locomotor activity (Fig. 2). Interneuron cross-talk and adaptive processes seem to be important factors in H₃R-mediated signalling.

Molecular Aspects The human histamine H₃ receptor (*hH₃R*) cDNA firstly described 1999 encodes a 445 amino acid protein and belongs to the histamine receptor family (H_{1–4}) superordinated to the large family of rhodopsin-like/class A G protein-coupled receptors (GPCRs). At all four receptors the endogenous ligand histamine acts as agonist. Whereas its affinity at *hH₁R* (*pK_i*=4.2) and *hH₂R* (*pK_i*=4.3) is quite low, it shows higher potency on *hH₃R* (*pK_i*=8.0) and *hH₄R* (*pK_i*=7.8).⁴⁹⁾ Comparison on protein level of the *hH₃R* (445) to *hH₁R* and *hH₂R* shows a moderate sequence homology of 22% and 20%, respectively.⁵⁰⁾ The *hH₄R* possesses a higher similarity to *hH₃R* with a sequence homology ranging from 38% up to 58% within the transmembrane domains.^{51–53)} Studies comparing the receptor pharmacology of *hH₃R* and *hH₄R* show remarkable differences in SAR of imidazole-containing ligands concerning affinity and efficacy^{49,54)} (Figs. 3, 4).

Species Differences As a result of cloning the H₃R of diverse species, like rat, mouse, Syrian hamster, guinea-pig and monkey, and other molecular biological approaches the knowledge about species-dependent H₃R pharmacology emerged.^{55,56)} With special focus on rat and human H₃R pharmacology binding data point out a significant variation in affinity of prototype H₃R ligands like thioperamide and ciproxifan. The unexpected existence of receptor heterogeneity among species leads to a sudden throwback of initial H₃R research programs due to radioligand binding assays based on rat brain homogenates.²²⁾ Mutational studies and a molec-

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Fig. 1. Brain Compartments Relevant for Histaminergic Innervations

Fig. 2. H₃R Auto- and Heteroreceptors

●, histamine H₁ receptor; ●, histamine H₂ receptor; ●, histamine H₃ receptor; ●, histamine; ●, G protein. cAMP: cyclic adenosine monophosphate; ctx: cortex; HDD: histamine decarboxylase; hip: hippocampus; hyp: hypothalamus; IP₃: inositol triphosphate; DAG: diacylglycerol; loc cor: locus coeruleus; na: nucleus accumbens; nbs: nucleus basalis magnocellularis; pvn: para-ventricular nucleus; sn(pr): substantia nigra (pars reticulata); str: striatum; vta: ventral tegmental area.

ular modelling approach identify two amino acids in the third transmembrane domain (TM3) of rat (*rH₃R*: Ala 119, Val 122) and human (*hH₃R*: Thr 119, Ala 122) receptors, which are thought to be in charge for pharmacological properties of H₃R ligands. In case of ciproxifan the exchange of residues 119 and 122 in rat sequence to the corresponding human amino acids Thr and Ala, respectively, consequently adjusts binding affinity.^{55,57,58)}

Splice Variants With respect to the genomic organisation of H₃Rs there is evidence for at least 20 splice variants

in human beings. Additional isoforms in rodents and guinea-pig are described on mRNA expression level.^{59–61)} Furthermore, a distinct protein expression in mouse and rat brain is proved by using isoform specific antibodies.⁶²⁾ No additional isoforms have been described in monkeys so far. While the physiological functions of most isoforms are still unknown, some exhibit a related pharmacology, for example in ligand binding, modulation of intracellular signalling ([³⁵S]GTPγS binding, cAMP and Ca²⁺ assays), and constitutive activity or even failed to show any biological response. Their respective

function in distribution and expression patterns with regard to the reported divergence of H₃R inverse agonist action might be relevant to generate H₃R heterogeneity. Expression of particular isoforms might be mediated by feedback mechanisms as *i.e.* the rat truncated non-functional H₃R isoform (lacking TM7) negatively influences expression of the functional rat H₃R isoform.⁶³⁾ Despite recent progress in clinical trials that show the therapeutic potential of H₃R inverse agonists/antagonists there is only modest information on isoform specific H₃R action.

Constitutive Activity Constitutive activity in both, recombinant expression systems and native tissues, emphasises the physiological relevance of H₃R as presynaptic autoreceptor controlling neuron activity.^{64,65} H₃R constitutive activity can be evidenced by signalling changes in transfected cell lines when compared to native tissues.⁶⁶ Activity extent varies depending on species, isoform, receptor density and cell lines. The molecular mechanism of constitutive activity might be attributed to a consensus motive (Arg-Leu-Ser-Arg-Asp-Arg/Lys-Lys-Val-Ala-Lys-Ser-Leu) on the carboxyl terminus in the third intracellular loop of H₃R, which is highly conserved among species.^{56,67} As tribute to the physiological concept of constitutive activity a reclassification especially of imidazole containing H₃R ligands takes place.^{10,68}

Signalling H₃R signalling is mediated through G_{i/o} proteins and hence, the receptor is negatively coupled to adenylyl cyclase (AC) in various H₃R transfected cell lines, according to former studies on rat brain homogenate, which show the influence of pertussis toxin in agonist-dependent stimulation of [³⁵S]GTPγS binding.⁶⁹⁾ Inhibition of cAMP formation consequently reduces downstream processing like activation of protein kinase A (PKA) and cAMP response element-binding protein (CREB)-induced gene transcription. H₃R mediated inhibition of cAMP levels is a mayor signalling pathway linked to histamine synthesis. Downregulation of cAMP-dependent PKA/extracellular signal-regulated kinase 1/2 (ERK1/2)/ets-like gene-1 (Elk-1) phosphorylation is associated with inhibition of cholangiocyte proliferation.⁷⁰⁾ In

cardiac synaptosomes and transfected cell lines H₃R induces attenuation of norepinephrine exocytosis. Similar findings suggest therapeutic potential of H₃R agonists in myocardial ischemia, leading to inhibitory effects on the Na⁺/H⁺ exchanger, voltage-operated Ca²⁺ channels and subsequent negative modulation of norepinephrine release.^{71–73}) H₃R associated G_{i/o} protein signalling also activates phospholipase A₂ (PLA₂) leading to the release of arachidonic acid and liberation of lipid mediators, which induce neuronal apoptosis and are associated with the progression of Alzheimer's disease (AD), ischemia or Parkinson's disease (PD).⁷⁴)

Additionally, mitogen-activated protein kinase (MAPK) and phosphatidyl inositol-3 kinase (PI3K) are activated. MAPK cascade influences cellular growth, differentiation and cell survival. Regarding the macroscopic level MAPKs have a pronounced effect on neuronal plasticity and memory consolidation.⁷⁵⁾ In several tumor-derived cell lines H₃Rs control proliferation by an autoinhibitory mechanism: while H₃R agonist imetit reduces cell growth, this effect can be reversed by clobenpropit. Maybe this action is associated to MAPK signalling cascade.^{76–79)} Interestingly, the protective effect on ischemia in cardiac sympathetic nerves is also hypothesized by the formation of a MAPK pathway *via* PLA₂, cyclooxygenase (COX), prostaglandin E₂ (PGE₂), in the end affecting prostaglandine EP₃ receptors (EP₃R).⁸⁰⁾ Stable transfected SK-N-MC cells and rat cortical neurons show both, constitutive and H₃R agonist-induced phosphorylation of protein kinase B (PKB or Akt), which results in the inhibition of glycogen synthase kinase-3 β (GSK-3 β). G β / γ subunit response *via* the PI3K/GSK-3 β axis is associated with physiological functions like memory consolidation or food intake.⁸¹⁾ By contrast, elevated levels of GSK-3 β can be found in brains of patients suffering from neurodegenerative disorders like AD^{82,83)} or schizophrenia⁸⁴⁾ as it induces apoptosis in (*i.e.* by amyloid plaque-) damaged cells.⁸⁵⁾ This protective effect is conversed by dysregulation of the PI3K/GSK-3 β axis, which might result from decreased levels of neurotransmitters like serotonin⁸⁶⁾ and histamine. In this case, the de-

Fig. 3. Imidazole-Based Histamine H₃ Receptor Ligands

velopment of neurodegenerative and metabolic diseases maybe follows from an overexpression of GSK-3 β . Modulation of intracellular Ca²⁺ release implicating H₃R activation is reported in different studies to act on PKA inhibition.⁸⁷⁾ Another suggestion is a direct interaction between G β / γ subunits and intracellular calcium stores.^{73,88)}

ANTAGONISTS

Imidazole-Based Antagonists as Pharmacological Tools

Antagonists and partial agonists have been achieved by structural enlargement of the endogenous ligand and agonistic lead compounds,^{11,89,90)} although transition is smooth. In the beginning of H₃R ligand development the imidazole was considered as essential element required for receptor affinity as firstly reported antagonists contain this aromatic heterocycle. Actually, compounds like thioperamide, ciproxifan, and clobenpropit (Fig. 3) are mainly used as reference structures because the basic ring holds diverse potential problematic issues, which increase the risk that these compounds are excluded from development as therapeutic agents. Nevertheless, all ligands can structurally be reduced to an alkylamine blueprint. Imidazole compounds potently bind at the heme iron of cytochrome P450 enzymes (CYP450).⁹¹⁾ When co-administered to other drugs, this may lead to drug–drug interactions and therefore, undesired side effects.^{92,93)} Another point of concern is that imidazole is a strong hydrogen bond acceptor and donor, respectively, what in some ligands might reveal reduced oral bioavailability and hampered brain penetration.⁹⁴⁾

Since the fourth histamine receptor has been discovered, selectivity and function of H₃R ligands is questioned and a reclassification of frequently used compounds takes place.^{10,49,95)} Instead of being a selective *h*H₃R antagonist **thioperamide** ($pK_i=7.2$)⁹⁶⁾ reveals comparable affinity at *h*H₄R (pK_i (*h*H₄R)=7.4).^{52,54,97)} Additionally, the compound possesses striking species differences with higher antagonist potency on rodent receptors (pK_i (*r*H₃R)=8.4).⁵⁸⁾ **Clobenpropit** proves to be a high affine *h*H₃R inverse agonist but also an *h*H₄R agonist. Although **ciproxifan** as well deals with discrepancies in rat and human receptor affinity and only shows moderate affinity to the human target ($pK_i=7.2$) the compound is one of the most frequently used reference structure because it possesses *h*H₃R preference (factor 13) as compared to *h*H₄R (Fig. 4). **Proxyfan** demonstrates a similar selectivity profile (ratio K_i (*h*H₃R)/ K_i (*h*H₄R)=13). Originally described as neutral antagonist⁵⁷⁾ it is reclassified as protean ligand^{98,99)} showing *in vitro* and *in vivo* an activity spectrum ranging from full agonism to full inverse agonism depending on the test system, the species and the degree of constitutive activity.¹⁰⁰⁾ Iodination and labelling of proxyfan in *para*-position of the phenyl rest leads to the radioligand [¹²⁵I]iodoproxyfan, which is due to its high affinity ($-\log K_D=9.0$)¹⁰¹⁾ used in binding assays.^{102,103)} Like proxyfan **cipralisant**, the former **GT-2331**, possesses protean ligand properties.¹⁰⁴⁾ After re-evaluation the chiral compound, firstly reported as 1*R*,2*R*-cyclopropyl eutomer ($-\log K_i=9.9$),¹⁰⁵⁾ occurs to be the dextrorotatory 1*S*,2*S*-enantiomer.^{106,107)} Nevertheless it has been the first ligand reaching clinical trials in the treatment of attention-deficit hyperactivity disorder (ADHD).¹⁰⁸⁾ Also **FUB 407**, an alkyl ether derivative of proxyfan, shows partial ago-

Fig. 4. Receptor Affinity Web-Profile for Imidazole-Based Reference Compounds

*r/h*H₃R: rat/human histamine H₃ receptor; affinities given as pK_i values.

nism *in vitro* (rat: $-\log K_i=8.0$; $EC_{50}=45$ nM; intrinsic activity (i.a.)=0.55). Surprisingly, *in vivo* investigations differ from these first results since the compound exhibits higher potency and maintains full agonism when administered *p.o.* to mice ($ED_{50}=0.3$; i.a.=1).^{109,110)}

Although actually imidazole-containing antagonists have less therapeutic relevance than non-imidazoles new structures are designed in order to use them as pharmacological tools, *i.e.* in the differentiation of the histamine receptor subtypes or clarification of molecular aspects. The combination of known scaffolds may lead to new potent ligands with improved physicochemical and pharmacological characteristics. Such an approach has been accomplished to obtain the antagonist **OUP-133** that incorporates structural elements of imifuramine, immepip, and cipralisant. It enhances histamine release to 180–190% of basal levels. Coadministration of the agonist immepip reverses this effect.¹¹¹⁾

Non-imidazole-Based Antagonists as Clinical Candidates As potent imidazole-containing H₃R antagonists exhibit above described possible drawbacks with respect to their drug-likeness, namely the risk of CYP interactions and unsatisfactory brain penetration, species differences for pre-clinical data and discrepancies in *in vitro* and *in vivo* efficacy, the newer H₃R antagonists contain a different basic moiety. A variety of secondary and generally tertiary amines, partly in form of aliphatic heterocycles, *i.e.* piperazino, pyrrolidino, 2-aminopyrrolidino, and morpholino elements,¹¹²⁾ was coupled instead of aromatic imidazole in order to find a suitable replacement structure. This resulted mostly in a piperidine moiety due to an increase in potency and decrease of pharmacokinetic interactions whereas larger substitutions or oxidation of this aliphatic heterocycle to some extent bears decline or loss in affinity.^{113–117)} The piperidinyl moiety and related structures have meanwhile been approved by numerous groups.^{118–121)}

One of the first and most prominent structures designed by such a replacement is the inverse H₃R agonist **tiprolisant**, the former **BF2.649** (Fig. 5), which shows high binding affinity ($-\log K_i=8.6$).¹²²⁾ The compound is now in phase II of clinical testing and targeted on narcolepsy, epilepsy and Parkinson's disease.¹²³⁾ Its imidazole-containing congener, FUB 181, is a potent ($-\log K_i=8.1$) and selective H₃R inhibitor improving wakefulness and learning.^{124,125)} Imidazole replacement leads to an improved drug-likeness and drug-

Fig. 5. Non-Imidazole-Based Histamine H_3 Receptor Antagonists

ability. Still, antitargets have to be considered carefully.¹²⁶⁾

Not only imidazole but also other *N*-heterocycles and unsaturated moieties show powerful CYP inhibition as shown in a series of cinnamic acid derivatives¹²⁷⁾ targeted on the treatment of obesity and diabetes mellitus.¹²⁸⁾ One of the most potent compounds, **NNC 38-1202** ($-\log K_i=8.3$), contains a 2-(pyrrolidinomethyl)pyrrolidino moiety. CYP inhibition is found to be 30% in CYP2D6, 31% in CYP3A4, and 66% in CYP1A2. Changing the pyrrolidinomethyl rest into a methylpiperidino group rectifies the situation with 3%, 12%, and 46% inhibition of CYP2D6, 3A4, and 1A2, respectively. Substitution of the chemical and metabolic unstable enamide of **NNC 38-1202** by an urea group further reduces CYP inhibition but at the same time affinity decreases to the power of ten ($-\log K_i=6.8$)¹²⁹⁾ (cf. Fig. 7). Regarding potency, similar SAR can be found in recently published spiro-isobenzofuranones coupled to (2-(piperidin-1-yl)ethyl)amide and -urea: these inverse agonists exhibit IC_{50} values of 0.54 nM and 21 nM, respectively.¹³⁰⁾ Related benzimidazole structures are WAY-361754 and analogs that exhibit improvement of cognitive functions in animal studies.¹³¹⁾

Enlargement of the alkylamine scaffold results in an amine-alkoxyphenyl one, which is related to that of the natural ligand **aplysamine-1**¹³²⁾ (Fig. 5). This bromotyrosine derivative extracted from the marine sponge *Aplysina* sp. (Verongidae) is one of the first non-imidazole antagonists, possesses moderate affinity ($-\log K_i=7.5$), and constitutes a

potential lead. In the development of H_3 R antagonists intense modifications of its two basic structures and the spacer length¹³³⁾ result in a great variety of diamine-based ligands.¹³⁴⁾ A simple, but fundamental structure is dipiperidine **JNJ-5207852** coming up as a preclinical candidate for sleep/wake and cognition disorders. JNJ-5207852 exhibits potent binding to rat ($pK_i=8.9$) and human ($pK_i=9.2$) H_3 R and a high selectivity over other GPCRs and ion channels. As a neutral antagonist it shows provigilant and procognitive effects in rodents.¹³⁵⁾ The second basic piperidine moiety boosts the affinity suggesting beneficial interactions with glutamic acid 206 in the receptor.^{136,137)} As a major drawback this structure hardly dissociates from the target and accumulates in brain showing full receptor occupancy after 24 h. Additionally, it induces phospholipidosis (lysosomal phospholipid storage disorder) in rats indicating drug-induced adverse effects, and hence JNJ-5207852 did not enter clinics and still proves to be an important lead structure.¹⁸⁾

A second natural antagonist that attracted attention as a lead structure is the non-aromatic steroid-related alkaloid **conessine** (Fig. 6). Regarding its affinity at hH_3R ($-\log K_i=7.2$) the compound is comparable to aplysamine-1 although hardly showing degrees of freedom. While researchers at Abbott Labs designed rigidized analogs of conessine (affinities in nanomolar concentration range),¹³⁸⁾ Arena Pharmaceuticals simplified the steroid skeleton by removal of several carbons, aromatisation of the central ring, and introduction of a

Fig. 6. Non-Imidazole-Based Histamine H_3 Receptor Antagonists

double bond in the bicycle while keeping the position of the aminergic centres (Fig. 6). Like JNJ-5207852 the resulting structurally related diamine-based compounds possess good affinities at rH_3R . A promising structure contains a pyrrolidine connected *via* an ethyl spacer to a phenyl core, which is substituted by a hexahydrocyclopenta[c]pyrrole moiety. In contrast to previously reported ligands the linker between amine and central core is shorter and no ether bridge but a double bond is inserted. This conessine derivative is an inverse agonist at the human receptor showing high potency ($-\log K_i=9.1$), selectivity, and a feasible pharmacological profile.¹³⁹ Further heterocyclic variations are shown with the dicyanoethylendiamine derivatives (imidazolidine compounds), piperazinoquinolines or aminoimidazoles in Fig. 6.

Combinations and modifications of these approaches lead to a great variety of compounds, and the majority of H_3R antagonist is more or less consistent with the amine-alkoxy-phenyl scaffold. Usually, it consists of a basic moiety, which is coupled *via* an alkyl spacer to a central core. This may be any heteroatom or -cycle that increases hydrophilicity. Variability is achieved through slight and distinct modifications of the amine moiety as well as a wide-spread substitution pattern of the central core: receptor affinity *in vitro* is maintained by insertion of either small polar, basic or acidic groups or larger lipophilic rests. Regarding this “eastern part” of the molecule, it seems that limitations only are given by the molecule’s size, related to Lipinski’s rule of five.^{140,141} In contrast, slight structural variations in the “western part” result in distinct pharmacokinetic and pharmacodynamic profiles deciding on the prospective role of a ligand (hit, lead, clinical candidate) and its possible therapeutic indication. A compilation of pharmacokinetic data regarding most of the furthest developed compounds can be found in Table 1.

While keeping the positions of the basic (piperidine) nitrogen and the phenyl rest in the amine-alkoxy-phenyl scaffold, larger modifications can be undertaken either in the

eastern part of the molecule or in the spacer. In comparison to JNJ-5207852 **JNJ-6379490** contains an imidazopyrimidine, which is bound to the piperidinepropoxyphenyl structure. Strictly speaking this is an imidazole-containing compound but, as the heterocycle is a different pharmacophore compared to the imidazole moiety of ciproxifan and related compounds, it is subsumed under the non-imidazole-based compounds. Insertion of the unsaturated heterocycle attenuates the basicity in aforementioned eastern part with the goal to decrease CNS accumulation. The compound possesses high potency ($pK_i=8.6$) as a neutral antagonist with good brain penetration (rat: $ED_{50}=0.2$ mg/kg intraperitoneally (i.p.)). It promotes provigilant effects *in vivo* in rodents, reduces cataplexy in the narcoleptic Doberman and even enhances short-term memory in rats. Unfortunately, it causes toxic effects in dogs and hence its development is stopped.¹⁸ Substitution of the ether group adhered to the spacer of JNJ-5207852 by an acetylene moiety leads to another affine antagonist, **JNJ-10181457** ($pK_i=8.9$).¹⁸ Probably due to conformational restriction or due to instability of the triple bond the compound indeed exhibits a shorter half life time and has therefore been evaluated as a positron emission tomography (PET) ligand. While *in vitro* autoradiography promises specific target labelling in brain regions with high receptor density, *in vivo* biodistribution studies show that this effect is due to a high degree of nonspecific binding.¹⁴² Another potential PET ligand is a recently reported **quinazolin-4-one** designed by Merck-Banyu. This inverse agonist exhibiting good overall pharmacokinetic properties to become a potent ($pK_i=8.2$), short acting ligand is a substrate of gp-1, which makes peroral application difficult.¹⁴³ More approaches to developing non-imidazole-containing PET^{144–146} or fluorescence ligands have been reported.^{147–149} Fluorescence-like ligands published by Schering Plough contain 2-(pyridin-2-yl)-1*H*-benzo[d]imidazoles added to the piperidine-propoxy-phenyl H_3R scaffold. The most affine structure of this series shows

high affinity ($pK_i=8.9$) and full antagonist properties at 0.1 nM^{150} (Fig. 5).

In **JNJ-7737782** the amine-alkoxy moiety is present as 1-isopropylpiperidin-4-yloxy residue. In order to establish new clinical candidates a series of compounds with sterically restricted propyloxy spacer has been prepared. In spite of a probable loss of affinity the reduction of rotatable bonds usually increases the drug-likeness of a compound. In the case of **JNJ-7737782**, open and rigidized spacers show comparable results in the ligand binding model. As second basic polar group adjacent to the lipophilic core piperidine ($pK_i=9.2$) shows higher affinity than the selected morpholine ($pK_i=8.7$). In both, **JNJ-10181457** and **JNJ-7737782**, researchers prefer the less basic and more hydrophilic morpholine for further pharmacological profiling because piperidine implicates a longer half-life, more extensive tissue distribution coming along with a toxic accumulation in CNS and/or cationic channel modulations. Indeed, the compound triggers arousal and wakefulness in rats, what turns it into a possible drug candidate for the treatment of attention disorders like ADHD.¹¹⁹ Besides, Johnson & Johnson holds another H_3R antagonist targeted on narcolepsy in phase II of clinical testing.¹⁵¹ Structure and detailed information on **JNJ-17216498** are awaited to be disclosed.

Another approach to rigidification of the molecular skeleton can be noticed in structures with bicyclic aromatic moieties. While **JNJ-7737782** exhibits a piperidine instead of the propyl chain, in **ABT-239** the ether bridge is enclosed in the aromatic core to form a benzofuran. Both compounds are conformational restrained but still show a certain degree of freedom as it is also true but even to a smaller extent for benzo[d]azepines like **GSK189254** (cf. **JNJ-5207852**→**ABT-239**→**JNJ-7737782**→**GSK189254** (Figs. 5, 6)).

As a bioisosteric replacement of piperidine a variety of pyrrolidines is used. In a series of biphenyls structure activity relationships reveal toxicity problems that emerge during drug development: here, **A-349821**, a dimethylpyrrolidine derivative, results to be the most potent compound ($pK_i=9.4$) (Fig. 5).¹¹⁸ In spite of an only moderate brain/blood ratio (0.5) that obviously arouses from its carboxamide moiety structure it possesses efficacy in cognition and especially ADHD models.¹⁵² Due to QT prolongation **A-329821** was sorted out from further development.²² To advance brain penetration the carboxamide is replaced by a nitrile group and after additional modifications of the basic moiety in the western part of the molecule a 3-(dimethylamino)pyrrolidine containing compound¹⁵³ is further characterized: **A-331440** is an inverse H_3R agonist with good affinity ($pK_i=8.6$) and high selectivity to the targeted receptor. Despite similar pharmacokinetic characteristics it differs from **A-329821** with regard to the brain/blood ratio (160). Surprisingly, **A-331440** does not show efficacy in cognition, but in obesity models: in mice it decreases body fat and reduces insulin tolerance as well as leptin level.¹⁵⁴ This is interpreted with a higher affinity to the long human receptor isoform ($-\log K_i=8.5$) than to the isoform, which is present in the human cortex and important for learning and memory functions ($-\log K_i=7.6$). Maybe interaction of ligands with different receptor isoforms explains the variety of possible indications for H_3R inverse agonists/antagonists.²² Development of **A-331440** is not continued due to genotoxicity but structure activity relations

to **A-417022** and **A-423579**, mono- and difluorinated analogs, respectively, show that substitution pattern strongly modifies toxic effects.¹⁵⁵

Biphenyls are also used in numerous series of GPCR ligands as privileged structures. Leaving out a polar group like the ether core they are bilaterally substituted *via* dimethylene or diethylene spacers with different aliphatic amines. Once more, piperidine has been proven to be the basic element of choice as it is easy to use in synthesis and it is an integral part in the most potent antagonists in this series, e.g. **4,4'-bis(piperidin-1-ylmethyl)biphenyl** ($pK_i=9.5$) (Fig. 6) and **4,4'-bis(2-(piperidin-1-yl)ethyl)biphenyl** ($pK_i=8.9$).¹²⁰ The methyl derivative seems to be more affine because, deduced from the computational model, the basic centres perfectly interact with the receptor's acids (Asp 114 and Glu 206). Due to its flexibility the ethyl derivative still fits to the binding pocket and therefore can keep the high potency. Enlargement of degrees of freedom by changing the aromatic biphenyl core into an alkyl chain implicates a slight loss of affinity as can be seen in aminobenzimidazole derivatives (Fig. 6).¹⁵⁶ Substitution of the aromatic biphenyl by imidazolidine and therefore insertion of a polar moiety is better accepted than an alkyl spacer connecting both basic centres. This is because of the additional facility to interact *via* π - π -bonding with the binding pocket (Tyr 115 and Trp 371). In a series of symmetrically substituted 2-(imidazolidin-2-ylidene)malononitriles (*S*)-2-(methyl)pyrrolidine results in more affine compounds ($pK_i=9.5$) compared to piperidine ($pK_i=8.6$).¹²¹ (Fig. 6) as it has previously been shown in other series.^{115,157}

The above mentioned benzofuran **ABT-239** shows structural overlap to the biphenylnitrile used in **A-331440** and the 2-(methyl)pyrrolidino group used in the malononitriles. Among a series of derivatives it is one of the most potent compounds ($pK_i=9.4$) and possesses good pharmacokinetic¹⁵⁸ and pharmacological properties in models of attention, cognition, and schizophrenia.¹⁵⁹ Clinical evaluation of the compound is not accomplished because of strong inhibition of human ether-a-go-go related gene (*hERG*) channels ($-\log K_i=6.7$). Blockade of these potassium channels leads to QT prolongation and arrhythmia. To minimize the toxic effects, which might arise from the lipophilic biphenylnitrile moiety (as naphthalene analogs of **ABT-239** evoke similar problems)¹⁶⁰ this group is changed into a variety of more hydrophilic heterocycles like nicotinonitrile (**A-698418**) or pyrazole (**A-688057**) rests. The resulting compounds exhibit comparable affinities ($pK_i=10.1$ and 9.3 , respectively) and pharmacokinetic data but at the same time a poorer brain penetration, obviously due to a loss of lipophilicity.¹⁶¹ At least, *hERG* inhibition is abolished.¹⁶²

Besides tiprolisant, some benzo[d]azepine derivatives, which are alkylated at the azepine nitrogen and in the eastern part substituted with aromatic amides *via* an ether bridge, exhibit the most promising and the furthest developed H_3R antagonists. A restricted 2,3,4,5-tetrahydro-1*H*-benzo[d]azepine pharmacophore gives rise to potent and highly selective ligands. The first designed benzo[d]azepine **GSK189254** ($pK_i=9.9$) is already in phase II of clinical studies for treatment of narcolepsy.¹⁶³ **GSK207040** is the pyrazin-2-carboxamide derivative of **GSK189254**, a comparable structure regarding receptor affinity ($pK_i=9.7$) and pharmacokinetics but with improved brain/blood ratio (3.5). It is envisaged acting

Fig. 7. Non-Imidazole-Based Histamine H_3 Receptor Antagonists

on cognitive disorders, *i.e.* dementia.¹⁶⁴ In contrast to the latter, **GSK334429** is a less rigidized 1,4-diazepane possessing comparable properties to that of GSK189254. It is active in attention and cognition models but what is more important, both, GSK189254 and GSK334429, have recently shown to be efficacious in models of neuropathic pain¹⁶⁵ pointing out a possible additive indication for these short-acting and poor brain penetrating ligands as H_3R modulates pain reception in the dorsal horn and spinal cord⁴⁸ (Fig. 7, Tables 1, 2).

Multiple Targeting Compounds The observation, that atypical neuroleptics stimulate histamine neuronal activity *via* blockade of serotonin 5-HT_{2A} receptors explaining the pro-cognitive effect of these drugs,¹⁶⁶ leads to diverse intelligent hybrid approaches, which are carried out in the H_3R field with one or another additional target.¹⁶⁷ Still, general challenges concerning the development of multiple ligands have to be overcome: in most approaches leads with the highest possible affinity on all targets are picked out, disregarding that especially in the central nervous system a modulatory effect is needed and a certain balance of affinities is more useful (*i.e.* when receptor densities or coupling mechanisms vary in different targeted compartments). This seems to be less complex the more similar the targeted structures are (*i.e.* two aminergic GPCRs) and the less related structures are found in the same compartment (in order to enhance selectivity). *In vitro/in vivo* relationships have to be sorted out as in the development of singular acting ligands, but achieving acceptable pharmacokinetic properties remains a major challenge, especially when molecules grow big. Due to this, combination of different pharmacophores by an integrative way is preferred over linking these elements with a spacer.^{168–170}

As the stimulating and attention-increasing effect of H_3R antagonists has been proven for many substances a dual mode of action by targeting H_3R and serotonin transporters (SERT) might be useful in the treatment of depression. Not only the mood-ameliorating but also the modulating effect on the concentration of other neurotransmitters involved in the pathophysiology of depression supports the linkage to selec-

tive serotonin reuptake inhibitors (SSRI). Overlapping fragments derived from H_3R antagonists (piperidine-propoxyphenyl scaffold), SSRIs (amino-tetrahydronaphthalene from sertraline), and wake-promoters (diphenylmethyl moiety from modafinil)¹⁷¹ leads to a series of compounds with tetrahydroisoquinoline and naphthyridine pharmacophores, respectively. Derivatisation of the H_3R affine piperidine,¹⁷² spacer rigidisation,¹⁷³ enlargement of the tetrahydroisoquinoline by annelating pyrrolidine,¹⁷⁴ and modifications of the diphenylmethyl substitution pattern¹⁷⁵ result in a great variety of substances. SAR show that **JNJ-2853867**, a 1,2,3,4-tetrahydroisoquinoline derivative, is the most promising compound. Interestingly, it holds a morpholine instead of the common piperidine in the H_3R fragment. The hybrid structure possesses good affinity to both, hH_3R ($-\log K_i=8.0$) and $hSERT$ ($-\log K_i=8.4$), and 30 fold selectivity over related aminergic transporters like norepinephrine (NET) and dopamine transporters (DAT). *Via* H_3R it mediates an increase of serotonin, dopamine, and norepinephrine levels in rat frontal cortex. Electroencephalography (EEG) measurements confirm a wake-promoting effect with reduction of rapid eye movement (REM) sleep. In the mouse tail suspension model, a classical test of antidepressant activity, JNJ-2853867 shows an effect after peroral administration to mice (3 mg/kg).¹⁷⁶ As these first preclinical results allocate, that H_3R /SERT hybrids are promising candidates currently developed for antidepressant therapy, the approach is broadened by accounting for moieties of fluoxetine and citalopram. In contrast to aforementioned tetrahydroisoquinolines the bi-cycle is opened but the aminoalkyl spacer rigidised¹⁷⁷ resulting in a series of piperazine and diazepane amides.¹⁷⁸

In order to enhance the procognitive effect of H_3R antagonists, additional inhibition of the histamine metabolising enzyme in brain, histamine N^T -methyltransferase (HMT), is thought to anticipate histamine metabolism, what results in a constantly increased level of the neurotransmitter in the synaptic cleft and therefore in a potentiated influence on other neurotransmitters.¹⁷⁹ A highly potent prototype of hybrid molecules targeting H_3R and HMT is **FUB 836** (hH_3R :

Table 1. Pharmacokinetic Data of Prominent H₃R Antagonists^{a)}

Name	Receptor affinity			Pharmacokinetics				Heteroreceptor function Increase of NT
	hH_3 p <i>K_i</i> / -log <i>K_i</i>	Function	ED ₅₀ (mice)	Brain/blood ratio	<i>t</i> _{1/2} (p.o. admin.)	Bioavailability	CYP450 interaction	
A-331440	8.5 (long isoform) 7.6 (cortex)	Inverse agonist		160	4 h (rat)	35% (rat)	No CYP inhibition but substrate	
A-349821	9.4	Inverse agonist		0.5	5.3 h (monkey)			
ABT-239	9.4	Inverse agonist		21.6 (1 h); 15.8 (5 h)	5.3 h (rat) 30 h (monkey)	53% (rat) 89% (monkey)	Inhibition of 2C9, 2D6; substrate of 3A4	Prefrontal cortex: ACh, DA
GSK189254	9.9	Inverse agonist	0.17 mg/kg p.o.	1	2.5 h (rat)	83% (rat)		Anterior cingulate cortex: ACh, DA, NE Prefrontal cortex: ACh, DA Dorsal hippocampus: ACh
GSK207040	9.7	Inverse agonist	0.03 mg/kg p.o.	3.5	2.9 h (rat)	88% (rat)		
GSK334429	9.9	Inverse agonist	0.35 mg/kg p.o.	0.5—0.8		91% (rat)		
Ketopiperazine (GSK)	9.2			0.2—0.3	1.2 h (rat) 4.3 h (dog)	48% (rat) 100% (dog)	No CYP inhibition	
GW-784568X	9.5				2 h (rat) 5 h (dog)	>50% (rat) >90% (dog)		
JNJ-10181457	8.9	Neutral antagonist	3 mg/kg s.c.					
JNJ-5207852	9.2	Neutral antagonist	0.13 mg/kg s.c.	Extensive brain penetration and accumulation	14.6—16.8 h (rats)	85—107% (rat)		
JNJ-6379490	8.6	Neutral antagonist	0.2 mg/kg i.p.					
JNJ-7737782	8.7	Antagonist						
Quinazoline-4-one (Merck-Banyu)	8.2	Inverse agonist		1.1		65% (rat) 28% (monkey)	No CYP inhibition	
Tiprolisant (BF2.649)	8.57	Inverse agonist	1.6 mg/kg p.o.	25	120 min (mouse)	84% (mouse)	CYP2D6 inhibition	Prefrontal cortex: ACh, DA

a) NT: neurotransmitter ACh: acetyl choline; DA: dopamine; NE: norepinephrine; p.o.: per os; s.c.: subcutaneously; i.p.: intraperitoneally

Table 2. Pharmacological Characteristics, Potential Indications and Hurdles in Development of H₃R Antagonists in Preclinics^{a)}

Name	Effects			
	CNS efficacy Locomotor activity Central side effects	Sleep/wake cycle	Attention and cognition	Epilepsy Depression Schizophrenia
A-331440				
A-349821	Dipsogenia ⊕ Spontaneous locomotor activity ○ Central side effects ○		Five-trial inhibitory avoidance ⊕ Five-choice SRTT ⊕	
ABT-239	Dipsogenia ⊕ Central side effects ○	Free-moving EEG ○	Five-trial inhibitory avoidance ⊕ Adult and aged social recognition ⊕ Spatial memory in two-choice water maze ∅ Passive avoidance ⊕	PPI of startle ⊕ N40 gating ⊕ Methamphetamine-induced hyperactivity ⊕ Catalepsy model ○
GSK207040	Dipsogenia ⊕ Central side effects ○		Passive avoidance ⊕	
GSK334429	Dipsogenia ⊕		Passive avoidance ⊕	
JNJ-10181457	Dipsogenia ⊕	Free-moving EEG: wakefulness ⊕ Narcoleptic Doberman ⊕	Passive avoidance ⊕	
JNJ-28583867	Imetit-induced drinking ⊕	Free-moving EEG: wakefulness ⊕		5-HTP induced head twitch ⊕ Mouse tail suspension ⊕
JNJ-5207852	Dipsogenia ⊕ Locomotor activity ○	Free-moving EEG: wakefulness ⊕ Narcoleptic Doberman ⊕	Passive avoidance ⊕ Water maze ⊕ Social discrimination ⊕ Acoustic fear conditioning ⊕	
JNJ-6379490		Free-moving EEG: wakefulness ⊕	Short-term memory ⊕ Social interaction ⊕	
JNJ-7737782		Free-moving EEG: wakefulness ⊕		
NNC 381202	Visible side effects ○			

Name	Effects		Data results	
	Pain	Food intake and body weight	Potential indication	Outcome
A-331440		Body fat, weight gain ⊕ Insulin tolerance, leptin level ⊕	Obesity Diabetes mellitus	Stopped due to genotoxicity
A-349821			Cognitive impairment	Stopped due to QT prolongation
ABT-239			Cognitive impairment Schizophrenia	Stopped due to hERG inhibition
GSK207040	Capsaicin-induced secondary allodynia ⊕		Cognitive impairment Neuropathic pain	Preclinics
GSK334429	Chronic constriction injury ⊕ Varicella-zoster-induced allodynia ⊕ Capsaicin-induced secondary allodynia ⊕		Cognitive impairment Neuropathic pain	Preclinics
JNJ-10181457		○	Narcolepsy Cognitive impairment Biomarker	Preclinics
JNJ-28583867			Depression	Preclinics
JNJ-5207852		○	Narcolepsy Cognitive impairment	Stopped due to brain accumulation and phospholipidosis in rats
JNJ-6379490			Narcolepsy Cognitive impairment	Stopped due to toxicity in dogs
JNJ-7737782			Narcolepsy ADHA	Preclinics
NNC 381202		Caloric intake ⊕	Obesity Diabetes mellitus	Stopped due to CYP interactions

a) ⊕, significant effect with positive outcome; ∅, not significant effect; ○, no effect.

$pK_i=10.0$; HMT: $IC_{50}=51$ nM), combining the H_3R piperidine-propoxyphenyl scaffold with aminoquinoline, which is a major synthon in HMT inhibitors like tacrine and amodiaquine. Substitution of the aminoquinoline moiety with cyclic or vinyllog amindines has led to improved potencies on either the receptor or the enzyme,¹⁸⁰ whereas coupling of tacrine to the H_3R pharmacophore causes a comparable pharmacological profile (**FUB 833**; hH_3R : $pK_i=9.5$; HMT: $IC_{50}=48$ nM).¹⁸¹ Tacrine, besides its HMT obstruction, also inhibits acetyl- (AChE) and butyrylcholinesterases (BuChE) (HMT: $IC_{50}=110$ nM; AChE: $IC_{50}=105$ nM; BuChE: $IC_{50}=64$ nM). Enzyme inhibitions are improved in **FUB 833** (AChE: $IC_{50}=2.6$ nM; BuChE: $IC_{50}=8.8$ nM) meaning that the hybrid possesses a quadruple mode of action.¹⁸² This approach might gain importance in the treatment of dementia since acetylcholinesterase inhibitors are commonly used in the therapy of Alzheimer's disease.¹⁸³ Only recently it has been re-up-taken by modification of lead JNJ-5207852, which shows AChE inhibition in the low micromolar range (AChE: $IC_{50}=3200$ nM). Improvement is achieved by *para*-substitution of the benzylpiperidine with an ethylalcohol moiety, which eventually adopts the carbonyl of acetylcholine. The IC_{50} value of 350 nM is comparable to that of donepezil (AChE: $IC_{50}=160$ nM),¹⁸⁴ a reference drug on the market. Recent advances in the field of other multiple acting AChE inhibitors have been reviewed.¹⁸⁵ Another approach to improve the effects on learning and memory is the introduction of NO donating moieties in H_3R antagonists. Release of this neurotransmitter might on the one hand lead to a better absorption of a compound due to NO-dependent relaxation of blood vessels. On the other hand, it may exhibit a neuroprotective character. Furoxan- or nitroglycerine-containing imoproxyfan^{186,187} analogs have been reported.^{188–190}

Peripherally acting hybrid structures are realised by combining histamine H_1 with H_3 pharmacophores to treat nasal congestion in allergic rhinitis. Combinations with classical H_1 antihistamines have already been reported in the field of imidazole-containing ligands.^{191,192} This approach has been expanded to non-imidazoles: coupling of the piperidine-propoxyphenyl moiety to loratadine in a spacer approach results in compounds with subnanomolar affinity on hH_3R and low nanomolar on hH_1R .¹⁹³ Compounds targeted on "hay fever" assuming a dual mode of action are recently reported **ketopiperazines**. Linking this heterocycle to a methylpyrrolidinepropoxyphenyl rest and substituting it with a difluorobenzoyl group (Fig. 7) leads to a poorly brain penetrating, highly affine compound on hH_3R ($pK_i=9.2$). This indicates a new peripheral approach since hH_1R affinity ($pK_i<5.6$) is almost completely lost.¹⁹⁴ Another ketopiperazine compound, **GW-784568X** ($pK_i=9.5$), is patented as a development candidate in a particular application and has already passed a clinical phase I/II study purposed on safety and efficacy of intranasal application in patients with allergic rhinitis^{195,196} (Fig. 7). Besides, GlaxoSmithKline holds two more H_3R -related compounds in clinical testing, namely GSK1004723 and GSK835726. Both are H_1R/H_3R dual antagonists and targeted on allergic rhinitis. Whereas a phase I safety study with intranasally administered GSK1004723 has been completed, a comparable investigation of orally applied GSK835726 is planned.^{197,198}

POTENTIAL INDICATIONS

Sleep-Wake Disorders Histaminergic neurons have numerous functions throughout the brain due to different projection areas and receptor cross-talk.⁷⁾ In the tuberomammillary nucleus (TMN) they function as pacemaker firing with low frequency. Firing rates vary to some extent according to the arousal state and they determine H_3R occupancy: while neuron activity is high during periods of waking and attention, it is even absent during sleep.¹⁹⁹ A low level of cumulative wake activity is linearly correlated with up to 80% of H_3R occupancy, whereas with higher levels of occupancy different additional effects take place.²⁰⁰ Afferent GABAergic innervation from the ventrolateral preoptic area (VLPO) proves to be in charge for inhibition during sleep (cf. Fig. 1). The GABA-mediated inhibition of TMN neurons is negatively controlled by $GABA_B$ receptors located at the GABA releasing nerve endings. Direct action of histamine on $GABA_A$ receptors seems to be histamine receptor-independent on an allosteric binding site.²⁰¹ As the TMN is mutually connected to aminergic, orexinergic and other nuclei, noradrenaline and several peptide neurotransmitters are able to influence GABA release. The absence of orexinergic neuron activity may result in the development of narcolepsy and related disorders.²⁰²

Narcolepsy is a rare sleep disorder with a minor prevalence of 0.02–0.05% generally attended by high levels of psychological strain. Whereas the systematic progress of the disease is difficult to describe, first symptoms appear in form of excessive daytime sleepiness (EDS), either on its own or accompanied by manifestation of cataplexy. The pathophysiology of narcolepsy is strongly associated with an early loss of orexinergic neurons in the hypothalamus liberating hypocretin, an excitatory neurotransmitter promoting wakefulness.²⁰³ Data from animal models underline the hypothesis that abnormal hypocretin transmission causes narcolepsy.^{204,205} Studies on the physiological and neurochemical relation of co-localised neurons mediating differences between sleep and alertness emphasise the role of a divergent discharge pattern of "REM-off" cells in cataplexy of narcoleptic Doberman.^{206,207} In this concept histaminergic neurons are linked to forebrain arousal, whereas serotonergic and noradrenergic neurons are associated with muscle tone and motor activity. Cataplexy is probably generated by an imbalance of neuronal activity: histaminergic cells fire at a level similar to wakefulness, whereas serotonergic and noradrenergic cells decrease activity.²⁰⁸

First hints at the role of the histaminergic system on maintaining waking state in the CNS were provided by the occurrence of unwanted sedative effects after administration of classical H_1R antihistamines. Based on the early work of Economo there is evidence for distinct histamine-connected wake promoting areas in the posterior hypothalamus and regions in the preoptic area associated with sleep.²⁰⁹ Subsequent lesion studies confirm this prediction and neurons in the posterior hypothalamus are proven to innervate wakefulness, whereas distinct experimental destruction or inactivation results in somnolence and hypersomnia.^{210–213} Early studies in cats on H_3R function show a significant relation between sleep decrease and attenuation after administration of H_3R inverse agonists and H_3R agonists, respectively. Thi-

operamide enhances cortical activation and wakefulness, while the contrary effect occurs after application of BP2-94, a H₃R agonist prodrug²¹⁴: agonist stimulation evokes cortical slow activity and increases slow wave sleep.²¹⁵ The general pattern of wake promoting activity of H₃R inverse agonists was observed in cats, mice, rats, and guinea pigs.^{122,216,217} Histaminergic neurotransmission promotes waking and alertness, while long term abolition of histamine synthesis in histidine decarboxylase knockout mice (KO) impairs the EEG and is accompanied with adverse effects on quality of sleep and waking state.²¹⁶ Consequently, mice lacking H₃R are insensitive to wake-promoting effects of thioperamide.²¹⁸

First preclinical and clinical data of a new class of wake promoting H₃R non-imidazole based antagonists/inverse agonists with almost drug-like properties like tiprolisant and JNJ-10181457 emphasises its therapeutic potential in sleep-wake disorders. These drugs show remarkable features, comparable with aforementioned prototype H₃R inverse agonists (ciproxifan, thioperamide), namely prolonged wakefulness accompanied with cortical activation (*c-fos* expression) and enhanced cortical EEG rhythm. They do not produce any alteration in behaviour and locomotor activity as compared to that of other wake-promoting drugs like caffeine, amphetamine or methylphenidate.¹⁸ Tiprolisant shows pronounced selectivity over a variety of other targets, as well as good distribution and brain penetration (ED₅₀ in mice=1.6 mg/kg *p.o.*; brain/blood ratio=25) and promotes an elevation of dopamine (133%) and acetylcholine (193%) concentration in rat prefrontal cortex indicating its benefit in the treatment of sleep disorders and cognitive impairment. Indeed, several preclinical trials have been accomplished, which emphasise its wake-promoting effect: in cats, tiprolisant causes total cortical activation.¹²² In orexin^{-/-} mice, cortical arousal is increased, while episodes of direct rapid eye movement (DREM) sleep onset from wakefulness are reduced. Interestingly, synergistic effects are found when co-administration of modafinil takes place.²¹⁹ Problems in clinical development eventually could arise from CYP2D6 or *h*ERG channel inhibition.^{24,126} First human data support a profit for narcoleptic patients: a pilot, placebo-controlled, single-blind, multi-center study, including 22 patients quoting an Epworth Sleepiness Scale (ESS) of 17.55 (max 24), reveals a significant reduction of EDS. Once a day treatment with 40 mg of tiprolisant during one week normalised ESS in nine patients (under 11), whereas the mean score of 21 patients was reduced to 11.81.²¹⁹ Both, preclinical and clinical data indicate that H₃R inverse agonists/antagonists constitute a novel class of drugs effective in EDS. Tiprolisant from Bioprojet received orphan drug status by the European Medicines Agency (EMA) in May 2007. Besides tiprolisant another H₃R antagonist has passed first clinical investigation in narcoleptic patients: JNJ-17216498 has not only been evaluated with regard to its safety and efficacy in sleep-wake disorders but also been compared to modafinil.¹⁵¹

Although there are hints that elevated levels of norepinephrine beneficially influence the rate of cataplectic attacks in narcolepsy,²⁰⁶ the exact mechanism of action of the ant-cataplectic effect of H₃R modulators remains to be evaluated.

Epilepsy Epilepsy is a chronic neurological disease that afflicts 1% of the population. The complex clinical appear-

ance is characterized by frequently and spontaneously occurring seizures, which in general are associated with neuronal hyperactivity. The imbalance of excitatory and inhibitory neuronal processes in glutamatergic and GABAergic neuronal systems is linked to the pathology of epileptic seizures. This alteration also might be modulated by various neurotransmitter systems affecting these two major pathways.²²⁰

Due to the appearance of pro-convulsive side-effects after systemic administration of H₁R antagonists one deduces that the neuronal histaminergic system affects epileptic seizure disposition.²²¹ Rodent studies report that elevated brain histamine levels, evoked by administration of histamine, the HMT inhibitor metoprine or L-histidine suppress epileptic discharges.^{222–226} Consequently, the histidine decarboxylase inhibitor α -fluoromethylhistidine reduces seizure threshold. The anticonvulsive effect of central histamine is attenuated by H₁R antagonists, while no changes have been observed after co-administration of H₂R and H₃R antagonists.^{223–225} With respect to the anticonvulsive effects of H₃R antagonists various studies report the beneficial use in distinct seizure models, *e.g.* electrically induced convulsions,^{227,228} kindling,^{229,230} and pentylenetetrazole- (PTZ) induced seizures.²³¹ From additional studies in mice it is deduced that combinatory application of selective H₃R antagonists and common antiepileptic drugs (AEDs) could provide protection against maximal electroshock- (MES) and PTZ-induced seizures.²³²

H₃R antagonist tiprolisant has been tested for its potential therapeutic benefit in three different animal models of epilepsy¹²³: it significantly attenuates number and duration of spike-and-wave discharges in the EEG of genetic absence epilepsy rats from Strasbourg (GAERS; 20 mg/kg *i.p.*).²³³ Moreover, in mice the compound protects against MES²³⁴ and reduces the cumulated period and number of hippocampal discharges in kainate-induced temporal lobe epilepsy (TLE)^{220,235} during the first 40 and 60 min after *i.p.* administration of 10 mg/kg and 20 mg/kg, respectively. Regarding the combined application of tiprolisant and AEDs, no changes in motor coordination and motor behaviour is observed in mice on the rotarod test.^{123,236} Beyond this promising preclinical data, tiprolisant has entered clinical phase II to evaluate the antiepileptic efficacy in a first single-blind study with 12 patients suffering from photosensitive epilepsy (PSE). PSE is a generalised form affecting about 5% of all epilepsy patients. It is defined by seizures that are continuously triggered by visual stimuli. Tiprolisant has shown a dose-dependent (20–60 mg single dose) alleviation of photo paroxysmal response (PPR) with or without concomitant administration of AEDs. The effect occurs 1–2 h post application and endures from 8 h up to 36 h.¹²³ One might expect that H₃R antagonists, alone or in combination with AEDs, contribute to the treatment of epilepsy, especially in patients with inadequate response to the conventional therapy.

Cognitive Impairment Impaired cognitive function is present in a broad range of neuropsychiatric diseases including AD, ADHD, and schizophrenia. The concept for H₃R antagonists in the treatment of cognition deficits is rather complex and correlates with effects on the sleep-wake cycle. Histamine mediates attention and vigilance upon stimulation of postsynaptic H₁Rs and H₂Rs in CNS.²³⁷ H₃R antagonists subsequently increase levels of histamine in distinct brain regions. Histaminergic neurotransmission in the TMN leads

to activation of secondary pathways projecting into different brain areas associated with cognitive functions. According to initial preclinical studies of novel H₃R antagonists (*e.g.* ABT-239, GSK189254, JNJ-10181457, and tiprolisant) enhanced acetylcholine levels by application of H₃R antagonists restore impaired cognitive functions.^{18,159,163,238} A direct correlation between histaminergic neurotransmission and cognitive impairment is controversially discussed due to different findings regarding histamine levels in brain compartments of AD patients. This might be related to the extent of neuronal apoptosis and course of disease.²³⁹ Differences on H₃R expression levels in the medial temporal cortex have been observed between brains of healthy persons and patients suffering from AD, what is consistent with the involvement of H₃R in cognition deficits.¹⁶³ H₃R antagonists demonstrate efficacy in numerous models of impaired learning. Data from rodent studies demonstrate the probable beneficial use and a few compounds have passed first steps into clinical investigation: ABT-834 in phase I studies is targeted on cognition disorders and GSK239512 is in phase II studies for dementia.²⁴⁰ Whereas most preclinical and clinical investigations focus on cognitive diseases and are thought to affect AD, H₃R antagonists show a broad efficacy in rodent models on other cognitive domains, such as attention and impulsivity, likely to be important for treatment of cognitive impairment going along with ADHD or schizophrenia (detailed review²⁴). MK0249 is a H₃R antagonists,²⁴¹ which is under investigation for a variety of indications: it has achieved phase II of clinical testing for ADHD,²⁴² AD,²⁴³ cognitive impairment in schizophrenia,²⁴⁴ and refractory EDS in patients with obstructive sleep apnea/hypopnea syndrome (OSA/HS).²⁴⁵ Also PF-03654746 is in phase II for ADHD.²⁴⁶ Additionally, this compound is tested in patients with allergic rhinitis²⁴⁷ and as a PET ligand.²⁴⁸ With JNJ-31001074 (structure undisclosed), a compound in phase II of clinical studies on in adults with ADHD,²⁴⁹ it is not clear if it is a H₃R antagonist.

Schizophrenia Schizophrenia is a chronic brain disorder, with a lifetime risk of 1%. It is structurally and functionally coupled to several cortical and subcortical brain regions participating in cognitive, emotional and motivational behaviour.²⁵⁰ Psychotic symptoms are divided into positive, such as delusion, hallucinations and disorganised speech, and negative symptoms, *e.g.* emotional pauperism and lack of motivation. Though the aetiology of schizophrenia regarding genetic and molecular biological aspects is hardly understood, dysregulations in dopamine and other neurotransmitter systems are involved in the development of the disease. Today, treatment of schizophrenia focuses on several typical and atypical neuroleptics, which mainly act as negative dopamine modulators in CNS. Their effect can be mediated by dopamine D₂-like receptors (D₂R, D₃R), serotonin receptor (5-HT_R) subtypes and/or the influence on the glutamatergic system.²⁵¹ Especially atypical compounds show equivalent affinities at D₂R/D₃R and 5-HT_{2A}R/5-HT_{2C}R. 5-HT₂R subtypes modulate dopamine levels in the corresponding neuronal systems: in tuberoinfundibular and nigrostriatal tracts exclusive D₂R/D₃R antagonism may evoke an increase of negative symptoms and also of extrapyramidal motoric and other side effects. 5-HT₂R antagonism attenuates the dopaminergic inhibition, while it continues in mesolimbic and mesocortical pathways, where no 5-HT₂Rs are expressed.²⁵² Stim-

ulation of dopamine release in the prefrontal cortex is associated with a therapeutic benefit in treating negative symptoms and cognitive impairment in schizophrenia.²⁵³ Due to rising therapeutic resistance and inadequate treatment of negative symptoms there is a large unmet medical need.²⁵⁴

As histaminergic neurons innervate brain areas strongly associated with the development of schizophrenia H₃R antagonists may influence its pathophysiology. In psychotic patients a significant increase in *N*^ε-methylhistamine levels in cerebrospinal fluid can be observed,²⁵⁵ whereas H₁R density decreases in cortical areas.²⁵⁶ Comparable data concerning histaminergic neuron activity is collected from schizophrenia models in rodents: methamphetamine-treated rats and mice rapidly exhibit locomotor sensitisation, accompanied by an enduring histaminergic signalling into the TMN. Mice receiving phencyclidine, an NMDA receptor antagonist, which induces antipsychotic symptoms, develop a similar histamine turnover in the brain.²⁵⁷ Although there is a general acceptance to extrapolate animal behaviour in models relevant for schizophrenia, studies on patients are essential to consider all criteria of the complex human pathophysiology.

To reveal efficacy and potency of antipsychotic drugs in preclinics a prepulse inhibition (PPI) deficit is induced by chronic treatment of D₂R stimulating agents. Alternatively, DBA/2 and C57EL/6 mice, which exhibit a natural occurring deficit of PPI, are used. Studies on thioperamide and ciproxifan confirm the antipsychotic-like profile of H₃R antagonists as both improve deficits in sensorimotor gating in a PPI of startle model and reduce methamphetamine-induced psychomotor hyperactivity.²⁵⁸ Tiprolisant, ABT-239, and GSK-189254 increase dopamine concentration in rat prefrontal cortex and have passed relevant tests in rodent schizophrenia models.^{122,159,163} In clinical studies tiprolisant shows efficacy in patients suffering from antipsychotic-induced weight gain and hence might be useful for standard co-medication.¹²³ ABT-239 is an important lead in the development of clinical candidates targeted on schizophrenia as it possesses promising pharmacokinetic properties^{259,260} (Table 1). After 1 h a brain/blood ratio of 21.6 is determined. Selectivity over a variety of GPCRs and ion channels is approved except for hα_{2C} (pK_i=7.2) and no CYP inhibition is noticed unless the compound acts as a substrate of CYP3A4.¹⁵⁸ Due to enhancement of dopamine and acetylcholine in rat prefrontal cortex, ABT-239 has been investigated in diverse models for attention, cognition, and schizophrenia.¹⁵⁹

Obesity Pharmacological studies reveal the influence of hypothalamic histaminergic neurons, which interfere with orexigenic pathways, on feeding behaviour and energy homeostasis and bear out in a positive effect of H₃R ligands in the treatment of metabolic diseases like obesity and diabetes mellitus.^{261,262} Elevated levels of central histamine, evoked by injection or even oral administration of L-histidine, reduce food intake and body weight in rodents.²⁶³ Experiments on knockout mice with a H₁R²⁶⁴ or HDC²⁶⁵ deficit show prevalence for hyperphagia, obesity and diabetes. Furthermore, several classical H₁R antagonists and antipsychotic drugs with H₁R affinity are known to increase feeding in rodents and cause weight gain in humans.^{266–268} These results suggest that central downstream H₁R signalling effects energy intake and contributes to the development of obesity and diabetes, whereas the role of H₃R ligands in the treatment of

Table 3. Pharmacological Characteristics of H₃R Antagonists in Clinical Studies^{a)}

Name	Effects				
	CNS efficacy Locomotor activity Central side effects	Sleep/wake cycle	Attention and cognition	Epilepsy Depression Schizophrenia	Pain
GSK189254	Dipsogenia ⊕		Passive avoidance ⊕ Water maze ⊕ Object recognition ⊕		Chronic constriction injury ⊕ Varicella-zoster-induced allodynia ⊕
Tiprolisant (BF2.649)	Spontaneous locomotor activity ○	Free-moving EEG: wakefulness ⊕ Cortical activation in orexin -/- mice ⊕ Cortical activation in cats ⊕ EDS in narcoleptic patients ⊕ Photosensitive seizures ⊕	Two-trial object recognition ⊕ Scopolamine-induced deficit ⊕	MK 801-induced motor hyperactivity ⊕ Methamphetamine-induced hyperactivity ⊕ Apomorphine-induced PPI ⊕ EEG in GAERS ⊕ Kainate-induced epilepsy ⊕ Maximal electroshock seizures ⊕ Rotarod test ⊕	

a) ⊕, significant effect with positive outcome; ∅, not significant effect; ○, no effect; preclinical data from animal models; human data from clinical trials in bold.

Table 4. Potential Indications and State of Development of H₃R Antagonists in Clinical Studies

Name	Data results	
	Potential indication	Status
ABT-834	Cognitive impairment	Phase I (Alzheimer's disease)
GSK189254	Narcolepsy	Phase I (dementia)
	Cognitive impairment	Phase I (hyperalgesia vs. duloxetine)
	Neuropathic pain	Phase II (narcolepsy)
GSK239512	Cognitive impairment	Phase I (dementia)
		Phase I (PET imaging)
		Phase II (Alzheimer's disease)
GSK835726	Allergy	Phase I (allergic rhinitis)
GSK1004723	Allergy	Phase I (allergic rhinitis)
GW-784568X	Allergy	Phase I/II (allergic rhinitis)
JNJ-17216498	Narcolepsy	Phase II (narcolepsy)
MK0249	Narcolepsy	Phase II (EDS in patients with OSA/HS)
	Cognitive impairment	Phase IIa (cognitive impairment in schizophrenia)
		Phase II (Alzheimer's disease)
		Phase II (ADHD)
PF-03654746	Cognitive impairment	Phase I (PET imaging)
	Allergy	Phase II (ADHD)
		Phase II (allergic rhinitis)
Tiprolisant (BF2.649)	Narcolepsy	Phase II (narcolepsy)
	Epilepsy	Phase II (epilepsy)
	Parkinson's disease	Phase II (sleepiness in Parkinson's disease)
	Schizophrenia	Phase II (cognitive impairment)
	Cognitive impairment	

metabolic diseases is still unclear as results from different studies are inconsistent: blockade of H₃R seems to be beneficial in decreasing energy intake, body weight and plasma triglycerides. Most recent studies indicate that clobenpropit increases histamine release from hypothalamus and reduces energy intake in normal and leptin-resistant mice with diet-induced obese (DIO) during a period of 3 h.²⁶⁹⁾ In contrast, other investigations on DIO wild type mice show that thio-peramide increases, whereas the H₃R agonist imetit decreases food consumption and body weight.²⁷⁰⁾ Obviously, these effects of H₃R modulators are more complex and not only mediated by histamine release but regulated through a

variety of receptors and neurotransmitters, like neuropeptide Y and nociceptin, providing response to the orexigenic system.²⁷¹⁾ As observed in A-331440 and A-329821, specific isoforms interacting in different intensities with similar ligands, may have a distinct influence on efficacy in different pharmacological models.²²⁾ Following this substantial differences of preclinical outcome, further investigations have to prove the so far unclear concept of H₃R antagonists in the treatment of obesity and weight gain.

Neuropathic Pain The potential role of H₃R signalling on nociceptive processes is studied by H₃R agonists and antagonists in various preclinical models of acute and neuro-

pathic pain. Although beneficial effects of H₃R antagonists have been shown in the processing of pain sensation, some results are more related to acute pain and the clinical relevance of H₃R antagonists in neuropathic pain is questionable. Effects of H₃R agonists on different animal models are somehow conflicting: imetit and imipep cause allodynia and decrease hyperalgesia, respectively. Thioperamide shows antinociceptive efficacy in various models of acute pain and also attenuates morphine-induced analgesia.^{272,273} Opposing effects are observed in a model of neuropathic pain, depending on whether the compound is administered centrally or peripherally.²⁷⁴ Moreover, as thioperamide also shows affinity on H₄R^{54,275} the exclusive blockade of H₃R is requested to evaluate an effect of H₃R antagonists on neuropathic pain. However, recent studies on selective H₃R inverse agonists, GSK189254 and GSK334429, demonstrate efficacy in models of acute and neuropathic pain.^{164,165} In this context, autoradiography studies with [³H]GSK189254 show a distinct H₃R expression pattern in the dorsal horn of human and rat spinal cord and in human dorsal root ganglion. These areas are generally associated with neurochemical processes on nociceptive conduction by cross-linking peripheral and central pathways of sensitisation.¹⁶⁵ For GSK189254 (*h*H₃R: p*K*_i=9.9), activity in the peripheral neuronal compartment might be deduced from its low rat brain/blood ratio of 1. Here, the compound is able to increase acetylcholine, dopamine, and noradrenaline levels at the low dosages of 1 mg/kg, perorally administered to rats (ED₅₀=0.17 mg/kg). It shows a half-life of 2.5 h and 83% bioavailability in rat, indicating a potent and short acting ligand.¹⁶³ In a phase I study, safety and efficacy of GSK189254 has been investigated to demonstrate that the electrical hyperalgesia (EH) model can be extrapolated from animals to patients. The compound has been compared to duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI) and a standard medication in neuropathic pain.²⁷⁶

CONCLUSIONS

The potential role of H₃R antagonists for the treatment of various different CNS disorders accompanied by histaminergic dysregulation has been discussed since the development of the first imidazole-based ligands. Meanwhile, some pre-clinical and the very first clinical data of various H₃R research programs have been published. Non-imidazole H₃R inverse agonists with almost drug-like properties, e.g. tiprolisant, ABT-239, GSK189254, and JNJ-10181457, show distinct pharmacological profiles in preclinical animal models and clinical studies in narcoleptic and epileptic patients (Table 2). This reveals the possibilities of a therapeutic application of H₃R ligands in diseases like sleep-wake disorders, dementia, epilepsy, schizophrenia, depression, pain, and metabolic diseases, but also reflects the complexity of biological actions of histamine and its role in the neurotransmitter regulation systems.

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