Therapeutic Efficacy of a H4 Receptor Antagonist in Humans: A Milestone in Histamine Research

Roland Seifert
Institute of Pharmacology, Hannover Medical School, Hannover, Germany

Raible et al. (1994) reported on the presence of a histamine receptor in human eosinophils with properties dissimilar to the histamine H2 and H3 receptor but similar to the H4 receptor. At the change of the millennium, a number of academic and industry groups independently de-orphanized a G-protein–coupled receptor (GPCR) that is now known as the H4 receptor (see Hough, 2001, for the first review on the H4 receptor). Only very few of the groups that originally de-orphanized the H4 receptor are still working in the field, indicative of a disconnect between de-orphanization of a GPCR and the arduous and time-consuming (patho)physiologic characterization of a receptor.

The H4 receptor was also cloned from human eosinophils (O’Reilly et al., 2002). The presence of mRNA of the H4 receptor in cells of the immune system suggested early on a role of this receptor in inflammatory processes (Hough, 2001). There is an ongoing controversial discussion regarding which human immune cell types express the H4 receptor (for review, see Seifert et al., 2013). However, there is consensus in the research community that the H4 receptor is present in human eosinophils because at least five independent research groups have rigorously characterized the receptor in these cells functionally and pharmacologically (Raible et al., 1994; O’Reilly et al., 2002; Buckland et al., 2003; Ling et al., 2004; Reher et al., 2012a).

Rob Thurmond and colleagues from Johnson & Johnson Research and Development (now Janssen Pharmaceuticals, Inc.) in La Jolla, CA, have played a major role in the elucidation of the function of the H4 receptor and its therapeutic potential over the past 15 years. In a seminal 2004 article published in the *Journal of Pharmacology and Experimental Therapeutics*, Thurmond and collaborators provided a detailed in vitro and in vivo characterization of the first potent and selective H4 receptor antagonist, JNJ7777120 (Jablonski et al., 2003), that has become the most important experimental tool compound in the field (Thurmond et al., 2004). Critical for the development of the H4 receptor field was the fact that these investigators made the compound freely available to academic research groups, catalyzing a surge of research activities and highlighting the importance of collaboration between industry and academia in modern drug development. Subsequently, Thurmond’s group showed that JNJ7777120 alleviated symptoms in a murine pruritus model (Dunford et al., 2007). The suitability of the H4 receptor as a drug target was bolstered by data on H4 receptor knockout mice. At least three independent research groups corroborated the findings by Thurmond et al. (2007) regarding the role of the H4 receptor in pruritus (Rossbach et al., 2009; Suwa et al., 2011; Ohsawa and Hirase, 2012).

Recently, Thurmond et al. (2014a) have characterized the pharmacokinetic and pharmacodynamic properties of the potent and selective H4 receptor antagonist JNJ 39758979 in healthy humans. JNJ 39758979 has a very long plasma half-life (124–157 hours) and reduces histamine-induced shape change in eosinophils ex vivo. The ex vivo data fit excellently to the in vitro data obtained with isolated human eosinophils (Raible et al., 1994; O’Reilly et al., 2002; Buckland et al., 2003; Ling et al., 2004; Reher et al., 2012a) and highlight the importance of the eosinophil as an unequivocally identified human cell type expressing the H4 receptor.

In this issue, Thurmond and colleagues (Kollmeier et al., 2014) report that, in a randomized double-blind crossover study, JNJ 39758979 reduced histamine-induced pruritus in healthy (nonallergic) humans. In contrast, this H4 receptor antagonist did not reduce the histamine-induced wheal and flare reaction that is mediated by the H1 receptor. Thus, this study provides key proof-of-principle that the H4 receptor plays an important (patho)physiologic role in humans. Pruritus is a very important medical problem that, in many cases,
cannot be satisfactorily alleviated by H₁ receptor antagonists (Thurmond et al., 2014b). Pruritus occurs in eczema, psoriasis, allergic conjunctivitis, and allergic rhinitis (Thurmond et al., 2014b). In addition, pruritus is a symptom of liver disease and viral infections (Raap et al., 2011; Tomina and Takamori, 2013). Hence, the present study (Kollmeier et al., 2014) opens the door for future clinical studies on different forms of pruritus with H₄ receptor antagonists. It should be emphasized that, in the current study, only healthy male volunteers (mostly young or middle-aged Caucasians) were studied. It needs to be evaluated whether the efficacy of H₄ receptor antagonists in other ethnic groups, women, and children and in various diseases is different. It should also be noted that JNJ39758979 will not become a clinically approved drug because, in independent clinical trials, the compound, unfortunately, was found to induce agranulocytosis (Thurmond et al., 2014a), a life-threatening toxic effect. It is assumed that agranulocytosis is intrinsic to the chemical structure of the compound and is not attributed to an effect mediated via the H₄ receptor (Kollmeier et al., 2014; Thurmond et al., 2014a). Therefore, chemically distinct H₄ receptor antagonists will hopefully be devoid of the risk of agranulocytosis. As another consequence of these data, the pharmacophore of JNJ 39758979 should be avoided for future drug development, regardless of the target.

In the development of clinically useful H₄ receptor antagonists, one should also keep in mind that antagonists at certain biogenic amine receptors, including H₄ receptor antagonists (Nijmeijer et al., 2012; Seifert, 2013), may exhibit stimulatory effects on noncanonical β-arrestin-mediated signaling pathways. However, to this end, antagonist-mediated β-arrestin signaling has only been convincingly observed in recombinant systems but not in native human cells (Seifert, 2013). Our group has looked for noncanonical signaling of JNJ7777120 in human eosinophils but did not find evidence for such signaling (Reher et al., 2012a). Thus, the in vivo relevance of β-arrestin signaling remains elusive. Along the same line, we still do not yet know whether the high constitutive activity of the human H₄ receptor observed in recombinant systems (Schneider et al., 2009) has any in vivo relevance and whether inverse agonist activity contributes to the clinical effects of JNJ 39758979.

The study of Kollmeier et al. (2014) revealed only a partial therapeutic effect of the H₄ receptor antagonist on pruritus. This may be related to the dose or route of administration (here, the drug was applied orally). It is possible that local administration of an H₄ receptor antagonist may yield different results. Moreover, the combination of H₁ receptor antagonists plus H₄ receptor antagonists may reveal synergistic responses in pruritus, either upon systemic or local administration. In this context, for practical reasons, the development of potent dual H₁ receptor and H₄ receptor antagonists is an interesting but also a challenging goal (Wagner et al., 2014). In addition, there may be even more ramifications; in eosinophils, activation of the H₂ receptor reduces proinflammatory responses mediated by chemokine receptors and the H₄ receptor, and H₂ receptor antagonists (still widely used as over-the-counter medication for gastroduodenal reflux disease and gastroduodenal ulcer) potentiate H₄ receptor-mediated chemotaxis in eosinophils (Reher et al., 2012a,b). Accordingly, H₂ receptor antagonists may exhibit antipruritogenic effects as well.

Currently, among all classes of histamine receptor ligands, only H₁ receptor antagonists are available as local gel preparations for dermatological applications. To further develop this important area of pharmacological research, it would be most desirable if selective H₂ receptor antagonists became available as dermatological preparations. Local administration of compounds may also strongly reduce the risk of life-threatening toxicity such as agranulocytosis. In this context, it would be desirable to see future studies on pruritus that describe how dermatological preparations of selective H₁ and H₄ receptor agonists (for review on such compounds, see Seifert et al., 2013) selectively induce the wheal and flare reactions and pruritus, respectively, and how H₂ receptor agonists may be used to reduce pruritus symptoms. It is also worthwhile to explore β₂-adrenoceptor agonists as adjunct to H₄ receptor antagonists because activation of the β₂-adrenoceptors mediates anti-inflammatory effects and β₂-adrenoceptor agonists are already approved for asthma therapy (Yasui et al., 2006).

The article by Kollmeier et al. (2014) also raises the important question on which cell types(s) the H₄ receptor in humans is localized. A straightforward explanation for the data by Kollmeier et al. (2014) could be that histamine activates the H₄ receptor on pruritus-conducting sensory C-fibers. However, in humans, the H₄ receptor has not yet been identified on such fibers. Alternatively, histamine could activate eosinophils residing in the skin, and these cells release mediators that activate C-fibers. Lastly, it was postulated that the H₄ receptor is expressed in the brain (Strakhova et al., 2009; Connelly et al., 2009). Such studies largely hinge on the use of antibodies. However, in general, the specificity of biogenic amine GPCR antibodies and of histamine receptor antibodies is of great concern (Michel et al., 2009; Seifert et al., 2013). Electrophysiological studies regarding the presence of the H₄ receptor in the brain (Connelly et al., 2009) still await confirmation by independent research groups as well. In a congress report (no peer-reviewed follow up publication visible in PubMed as of May 15, 2014), no evidence for the presence of the H₄ receptor in brain could be obtained measuring stimulation of guanine nucleotide exchange and inhibition of norepinephrine release (Felszeg et al., 2012). A simple way of assessing a role of peripheral or central H₄ receptor in mediation of pruritus in humans is to compare the effect of H₁ receptor antagonist applied locally to skin or H₄ receptor (with capability of penetrating the blood-brain barrier) applied systemically.

The study by Kollmeier et al. (2014) needs to be commented for more general scientific reasons as well. First, this study is an excellent example of a GPCR, where de-orphanization has ultimately resulted in the development of a clinical drug candidate. Second, the study provides compelling documentation that translational success takes time (in this case 20 years from the initial pharmacological description of the H₄ receptor) and is based on solid molecular pharmacology and animal pharmacology research. Nowadays, many funding agencies put a lot of pressure on scientists, with respect to a translational research component, without sufficiently recognizing the eminent importance of solid basic research for success. Third, the study shows that, in the end, persistence and stamina in research pay off to achieve a scientific breakthrough. Virtually all of the original research on the H₄ receptor was published in high-quality academic journals but
not in journals with very high-impact factors. Hence, the success story of H4 receptor antagonist development is an excellent example that the impact factor of the journal where the research was published tells little about the actual quality and scientific impact of the research. Fortunately, there is now a momentum in the research community to de-emphasize the impact factor as a parameter for research quality (Pugh and Gordon, 2013), and the present case study for the H4 receptor can be used as a strong argument in this discussion.

Regardless of the future of H4 receptor antagonists as drugs for the treatment of pruritus, the present study by Kollmeier et al. (2014) has already made a very important contribution to our understanding of human physiology using an “experimental therapeutics,” with high selectivity for a clearly defined receptor. The article has a similar scientific importance as the identification of the first selective H2 receptor antagonists or selective H3 receptor ligands (Black et al., 1972; Arrang et al., 1987).

In conclusion, the development of H4 receptor story over the past 20 years shows that if pharmacological research is conducted stringently from the molecular level to the cellular, animal, and human levels, ultimately, experimental therapeutics emerge, providing a rational basis for the development of innovative drugs. I hope that this success story will lead to a revival of prematurely terminated orphan receptor research programs in the pharmaceutical industry. They may yield striking success stories. It is just a matter of rigorous basic pharmacological research, persistence, and stamina. The case has been made for the H4 receptor.

References


