Histamine 2 receptor

Shan, Ling; Swaab, Dick F

2025

DOI (link to publisher)
10.1016/j.xcrm.2025.102023

document version
Publisher's PDF, also known as Version of record

citation for published version (APA)
Shan, L., & Swaab, D. F. (2025). Histamine 2 receptor: Emerging target for the treatment of attention-deficit/hyperactivity disorder. *Cell reports. Medicine*, *6*(3), 102023. https://doi.org/10.1016/j.xcrm.2025.102023

Cell Reports Medicine

CellPress
OPEN ACCESS

Spotlight

Histamine 2 receptor: Emerging target for the treatment of attention-deficit/hyperactivity disorder

Ling Shan[1,*] and Dick F. Swaab[1]
[1]Department Neuropsychiatric Disorders, Netherlands Institute for Neuroscience, an Institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, the Netherlands
*Correspondence: l.shan@nin.knaw.nl
https://doi.org/10.1016/j.xcrm.2025.102023

A study by An et al. sheds a novel light on the potential role of histamine 2 receptor (H_2R) deficiency in attention-deficit/hyperactivity disorder (ADHD), which could be a future therapeutic target of ADHD. This spotlight provides an overview of the current knowledge of the histaminergic system and proposes future directions.

Neuronal histamine is synthesized from histidine through the key enzyme histidine decarboxylase in the tuberomamillary nucleus.[1] Brain histamine is reduced to its inactive form, tele-methylhistamine, by histamine N-methyltransferase (HNMT). Histamine exerts its functions via the four types of G protein-coupled histamine receptors (H_{1-4}Rs).[1] These receptors are involved in many basic physiological functions including attention, sensory and motor functions, cognition, learning, and memory.[1] These functions are impaired in patients with attention-deficit/hyperactivity disorder (ADHD), a neurodevelopmental disorder that is characterized by inattention and/or hyperactivity/impulsivity. However, there is very limited evidence linking ADHD to the histaminergic system. ADHD is in fact generally associated with and treated through the dopaminergic and noradrenergic system.[2]

Two retrospective studies[3,4] have identified a significant association between a history of histamine 1 receptor (H_1R)-antihistamine use and an increased risk of ADHD symptoms. In addition, a double-blind, placebo-controlled crossover trial showed that the HNMT polymorphisms modulated the effect of food additives on children's ADHD symptoms, an effect that was not present for catecholamine genes.[5] It should be noted that this evidence is rather indirectly connecting the histaminergic system to this disorder.

Interestingly, An et al.[6] recently highlighted a deficiency of histamine H_2 receptors (H_2Rs) in parvalbumin (PV)-expressing neurons of the substantia nigra pars reticulata (SNr) of ADHD human brains compared to those of controls. Although the H_2Rs were known for a long time to be expressed in the SNr region, this is the first time that H_2R deficiency in this brain region was connected to ADHD.

Furthermore, they demonstrated that this selective deficiency directly contributes to ADHD-like mouse behaviors, including hyperactivity in both open-field and home-cage tests, impulsivity and impaired sustained attention in the 5-choice serial reaction time task, and diminished responsiveness to bright light stimuli. In contrast to the previous opinion that prefrontal cortex dysregulation played a dominant role in ADHD,[7] An et al. provided evidence of the essential role of subcortical regions, particularly the involvement of H_2R in the nigrostriatal dopaminergic pathway, in maintaining sustained attention (summarized in Figure 1).

They further tested the potential of H_2R agonists as a promising pharmacological compound for ADHD treatment. Amthamine, an H_2R agonist, when bilaterally microinjected into the ADHD mouse model, could effectively reverse hyperactivity, impulsivity, and inattention. Traditional ADHD medicines, such as stimulants, often exhibit an inverted U-shaped effect, where therapeutic benefits significantly diminish when drug concentrations lead either to low or excessive levels of dopamine or noradrenaline.[2] An H_2R agonist with the ability to pass the blood-brain barrier could therefore be a promising treatment for ADHD. In addition, the modulation of attention and activity by H_2R in SNr PV^+ neurons was found to be unidirectional, as overexpression of H_2R in PV^+ neurons did not impact locomotion or attention, further excluding the risk of overdosing H_2R agonist in this brain region.

It is known that female ADHD patients exhibit lower ratings of hyperactivity, inattention, and impulsivity than male patients do.[8] Female patients showed considerably stronger symptoms related to emotional dysregulation than male patients did in both childhood and adulthood.[9] To gain a deeper understanding of gender-related treatment of H_2R, we recommend that future research could include female mice as well. This could provide a more comprehensive understanding of gender-specific treatment responses in ADHD. Ultimately, this knowledge may help to tailor treatment and disease management strategies to better meet gender-specific needs.

In summary, the current investigation from An et al. sheds a novel light on the potential role of H_2R deficiency in ADHD, which could deepen our understanding of the pathogenesis of ADHD and provide support for establishing a histamine-receptor-associated hypothesis. In addition to contributing to the development of new therapies for ADHD,[10] the study provides a novel and precise target for future therapy. Because ADHD patients with H_2R deficiency of PV^+ neurons in the SNr are at risk for disinhibition of SNr dopaminergic neurons and superior colliculus

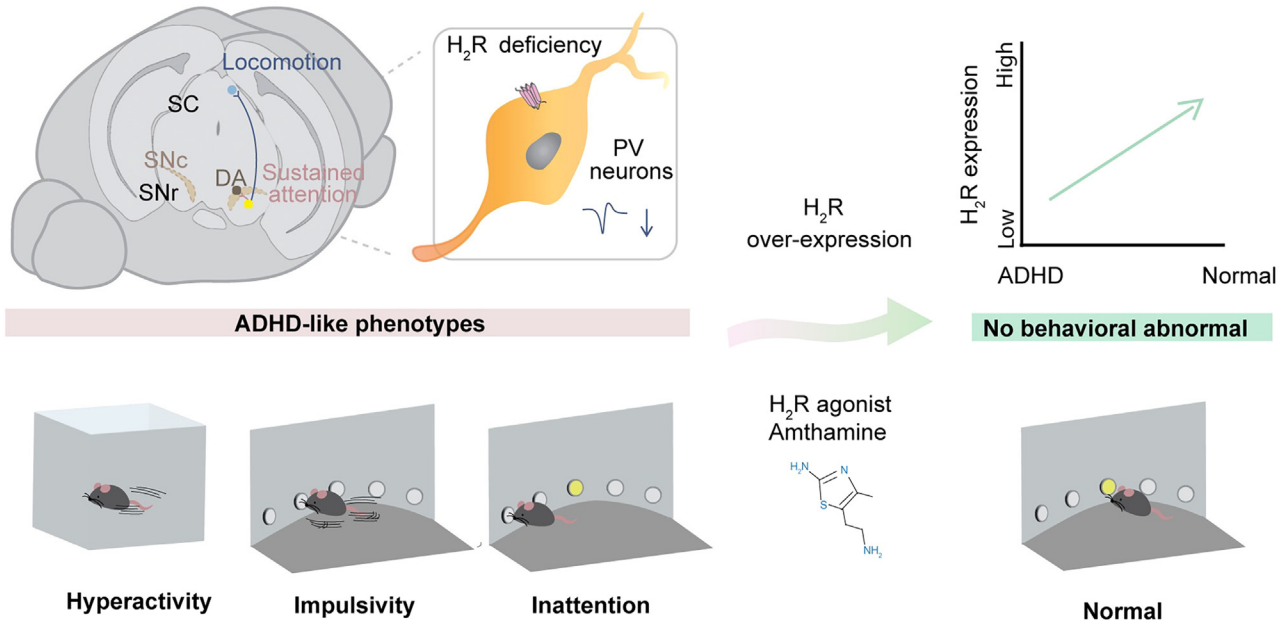

Figure 1. The mechanism of H_2R deficiency in PV^+ neurons with the pathogenesis of ADHD

neurons, H_2R may be a potential biomarker for clinical diagnosis of ADHD patients using H_2R-specific positron emission tomography ligands or functional magnetic resonance imaging to detect activity of those brain regions. This study highlights the need for further investigation into the role of specific changes, such as H_2R in age and sex dependency of ADHD; insight into the possible effects of the co-morbidities present in the human sample; and the need to develop effective H_2R-related interventions to treat (subgroups of) patients.

ACKNOWLEDGMENTS

The authors are grateful to Prof. Weiwei Hu from the Zhejiang University for providing valuable suggestions and Figure 1. Dr. L.S. and Prof. D.F.S were supported by the ALS Foundation Netherlands (AV20210014 and AV20240002) and Friends of the Netherlands Institute for Neuroscience Foundation.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Panula, P., Chazot, P.L., Cowart, M., Gutzmer, R., Leurs, R., Liu, W.L.S., Stark, H., Thurmond, R.L., and Haas, H.L. (2015). International union of basic and clinical pharmacology. XCVIII. histamine receptors. Pharmacol. Rev. *67*, 601–655. https://doi.org/10.1124/pr.114.010249.
2. Farhat, L.C., Flores, J.M., Avila-Quintero, V.J., Polanczyk, G.V., Cipriani, A., Furukawa, T.A., Bloch, M.H., and Cortese, S. (2024). Treatment Outcomes With Licensed and Unlicensed Stimulant Doses for Adults With Attention-Deficit/Hyperactivity Disorder A Systematic Review and Meta-Analysis. JAMA Psychiatry *81*, 157–166. https://doi.org/10.1001/jamapsychiatry.2023.3985.
3. Fuhrmann, S., Tesch, F., Romanos, M., Abraham, S., and Schmitt, J. (2020). ADHD in school-age children is related to infant exposure to systemic H1-antihistamines, https://doi.org/10.1111/all.14411.
4. Schmitt, J., Buske-Kirschbaum, A., Tesch, F., Trikojat, K., Stephan, V., Abraham, S., Bauer, A., Nemat, K., Plessow, F., and Roessner, V. (2018). Increased attention-deficit/hyperactivity symptoms in atopic dermatitis are associated with history of antihistamine use. Allergy Eur. J. Allergy Clin. Immunol. *73*, 615–626. https://doi.org/10.1111/all.13326.
5. Stevenson, J., Sonuga-Barke, E., McCann, D., Grimshaw, K., Parker, K.M., Rose-Zerilli, M.J., Holloway, J.W., and Warner, J.O. (2010). The role of histamine degradation gene polymorphisms in moderating the effects of food additives on children's ADHD symptoms. Am. J. Psychiatry *167*, 1108–1115. https://doi.org/10.1176/appi.ajp.2010.09101529.
6. An, D., You, Y., Ma, Q., Xu, Z., Liu, Z., Liao, R., Chen, H., Wang, Y., Wang, Y., Dai, H., et al. (2025). Deficiency of histamine H_2 receptors in parvalbumin-positive neurons leads to hyperactivity, impulsivity, and impaired attention. Neuron *113*, 572–589.e6. https://doi.org/10.1016/j.neuron.2024.12.002.
7. Hong, S.B., Zalesky, A., Fornito, A., Park, S., Yang, Y.H., Park, M.H., Song, I.C., Sohn, C.H., Shin, M.S., Kim, B.N., et al. (2014). Connectomic disturbances in attention-deficit/hyperactivity disorder: A whole-brain tractography analysis. Biol. Psychiatry *76*, 656–663. https://doi.org/10.1016/j.biopsych.2013.12.013.
8. Hasson, R., and Fine, J.G. (2012). Gender differences among children with ADHD on continuous performance tests: A meta-analytic review. J. Atten. Disord. *16*, 190–198. https://doi.org/10.1177/1087054711427398.
9. Gershon, J. (2002). A meta-analytic review of gender differences in ADHD. J. Atten. Disord. *5*, 143–154. https://doi.org/10.1177/108705470200500302.
10. Veronesi, G.F., Gabellone, A., Tomlinson, A., Solmi, M., Correll, C.U., and Cortese, S. (2024). Treatments in the pipeline for attention-deficit/hyperactivity disorder (ADHD) in adults. Neurosci. Biobehav. Rev. *163*, 105774. https://doi.org/10.1016/j.neubiorev.2024.105774.