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H_3R receptor antagonist in the discovery of antiseizure compounds

XQ Deng
Jinggangshan University, China

Statement of the Problem: Epilepsy is the second most common neurological disease after cerebrovascular disease. Chronic and recurrent epilepsy not only cause physical damage such as memory loss and emotional expression disorder, but also reduce the quality of daily life of patients, increasing their psychological burden and leading to a high proportion of accidental deaths. The third generation of antiseizure drugs (ASDs) represented by Eslicarbazepina and Brivaracetam showed better antiseizure effect, pharmacokinetics and safety. However, these drugs have not reduced the proportion of refractory epilepsy or exhibited trauma repair.

Methodology & Theoretical Orientation: With the application of target-based design in antiepileptic drug discovery, an increasing number of target-based antiepileptic active molecules have been discovered. The histamine H_3 receptor is a promising new target for antiepileptic treatment. The use of the histamine H3 receptor as a target for epilepsy treatment has been confirmed since 2001. Unfortunately, pharmacologists have not paid too much attention to it, and no antiseizure drug based on the histamine H_3 receptor was approved. This study is aim to discover new antiseizure drugs based on histamine H_3 receptor(H_3R).

Findings: The H_3R antagonist provided protection in MES-induced seizure model. What is more, H_3R antagonist repaired the damaged hippocampal neurons. Some antiseizure molecules has been identified from a large number of H_3R antagonists, and the antiseizure activity was positively related to their H_3R inhibitory on the premise of ensuring a certain lipid water partition coefficient. And their antiepileptic activity can be reversed by H_3R agonist RAMH.

Conclusion & Significance: H_3R is a potent target for the treatment of epilepsy. H_3R antagonist not only inhibit the seizure, but also repair the damaged hippocampal neurons coused by epilepsy. Discovery of new antiseizure drugs among H_3R antagonistss is practicable and encouraging.

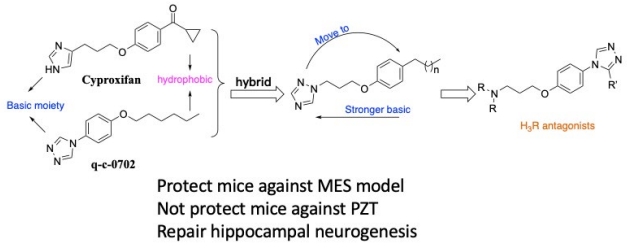

Figure 1: The antiseizure and nerve repair effects of H3R antagonists

Recent Publications:

1. Yokoyama H (2001) The role of central histaminergic neuron system as an anticonvulsive mechanism in developing brain. Brain Dev, 23: 542-547.
2. Sadek B, Saad A, Sadeq A, Jalal F, Stark H (2016) Histamine H_3 receptor as a potential target for cognitive symptoms in neuropsychiatric diseases. Behav Brain Res 312: 415–430.
3. Mingxia Song, Xianqing Deng (2020) Design, synthesis and anticonvulsant effects evaluation of nonimidazole histamine H_3 receptor antagonists/inverse agonists containing triazole moiety. Journal of Enzyme Inhibition and Medicinal Chemistry, 35: 1310–1321.
4. Jiangong Wang (2022) Histamine H_3R antagonist counteracts the impaired hippocampal neurogenesis in Lipopolysaccharide-induced neuroinflammation. International Immunopharmacology 110:109045.
5. Feng Xiao, Xianqing Deng (2020) Synthesis and antiseizure effect evaluation of nonimidazole histamine H_3 receptor antagonists containing the oxazole moiety. Arch Der Pharm. 354, 2000298.

Biography

Xianqing Deng is currently a Professor of Medicinal Chemistry in the Health Science Center of Jinggangshan University, China. He has been Head of the Department of Pharmacy from 2021, Director of Academic Sub-committee of Health Science Center from 2022. Dr Deng is expertised in organic medicinal chemistry and new drug design and discovery. His research focus on the design and synthesis of novel antiseizure, antibacterial and anticancer drugs. He is also interested in discovery and development of novel active substances from Traditional Chinese Medicine. He has authored more than 60 papers in international peer-reviewed journals and a current Hills Index of 20 (Web of science). He has been a guest editor of Frontiers in Chemistry and Molecules and a reviewer for more than 20 scientific journals.

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