Review Article

H3 antagonists and postoperative cognitive dysfunction

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Abstract

Since histamine (HA) was first synthesized in 1907 and isolated as a bacterial contaminant of an extract of ergot in 1910, its role in health and disease and its molecular mechanism of action have been unraveled, leading to the formulation of an array of drugs with immense therapeutic value. HA is produced by decarboxylation of histidine, and its biological actions are mediated through four HA receptors, namely, H_1, H_2, H_3, and H_4 based on their sequence, their link to differential intracellular signaling mechanisms, and their unique pharmacological properties. H_1 and H_2 receptors have been targeted for treating allergic conditions and peptic ulcers, respectively. The discovery of a third HA receptor subtype (H_3R) by molecular biologists in 1983, structurally a member of the G-protein-coupled receptor family, has led to the development of many potent and selective H_3 receptor antagonists having the potential to treat a wide spectrum of neurological diseases including postoperative cognitive dysfunction.

Keywords: Cognition, histamine H3 receptor, postoperative cognitive dysfunction

Introduction

Unlike the H_1 and H_2 receptors that have primarily peripheral actions, H_3 receptors are located on histaminergic nerve terminals in the brain. The histamine (HA) H3 receptor was first described as a presynaptic autoreceptor that is able to signal on its own, that is, without activation by an agonist, and thus displays constitutive activity. Later, it was shown to also function as a heteroreceptor. H3R activation inhibits synthesis of HA through adenylate cyclase/protein kinase A and calcium/calmodulin-dependent protein kinase type II pathways. In addition, it can activate phospholipase-A2-mediated release of arachidonic acid and phosphoinositol-3-kinase activity resulting in activation of Akt/glycogen synthase kinase (GSK)-3β axis. It modulates the release of other neurotransmitters (NTs) such as GABA, glutamate, dopamine (DA), norepinephrine (NE), 5HT, and acetylcholine (ACh), and thereby possessing stimulant and nootropic or cognition-enhancing effects.

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The Histaminergic System

The sole source of brain HA is neurons localized in the hypothalamic tuberomammillary nuclei. These neurons project axons to the whole brain and are organized into functionally distinct circuits influencing different brain regions and displaying selective control mechanisms.[1,2]

The histaminergic system is involved in basic physiological functions, such as the sleep–wake cycle, energy and endocrine homeostasis, sensory and motor functions, and cognition and attention. It also regulates basic homeostatic and higher functions, including arousal, circadian, and feeding rhythms. Brain HA plays a fundamental role in eating behavior as it induces loss of appetite and mediates satiety. HA regulates peripheral mechanisms such as glucose uptake and insulin function. Activating HA receptors in the hypothalamus influences thermoregulation, circadian rhythm, energy expenditure, and appetite.[3,4] The neuromodulator HA is released throughout the brain during periods of wakefulness, and the drug betahistine (an H_1 agonist/H_3 antagonist)

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counters the metabolic side effects associated with chronic antipsychotic treatment.[5-7]

HA plays an important role in multiple central nervous system (CNS) disorders including insomnia, narcolepsy, cognitive defects, sleep disturbances, Parkinson's diseases, schizophrenia, Alzheimer's disease, Tourette's syndrome, and cerebral ischemia. HA receptors are, therefore, being targeted for the treatment of many of these neurologic and psychiatric diseases.[8-11]

Pharmacology of H3 Antagonists

H_3R antagonists have a basic amine group linked to an aromatic/lipophilic region that is connected to a polar group or another basic group or a lipophilic region. Stimulation of presynaptic H_3 autoreceptors on histaminergic neurons by HA inhibits the synthesis of HA (through histidine decarboxylase) and also inhibits the release of HA from the neuron. Similarly, stimulation of presynaptic H_3 heteroreceptors on non-histaminergic neurons inhibits the release of a number of NTs, including NE, ACh, serotonin (5HT), DA, and others. These NTs can then activate their respective target receptors postsynaptically to evoke a variety of physiological responses.

H_3R antagonists containing an imidazole ring like thioperamide inhibit the cytochrome P450 isoenzymes [Figure 1]. They have limited penetration of the blood–brain barrier and too toxic to be clinically useful.[12] Non-imidazole H_3R antagonists reach the CNS more easily but have strong binding to hERG K^+ channel (the human E*ther-à-go-go*-Related Gene) that can lead to the potentially fatal long QT syndrome.[13] Betahistine (N-methyl-2-pyridylethylamine) is an H1 agonist and H3 antagonist that improves labyrinthine microcirculation by acting on the precapillary sphincters of the striavascularis. The drug is widely prescribed for vertigo, especially in Ménière's patients. It can also cause weight loss. Pitolisant, an antagonist/inverse agonist, is orally effective and is highly selective for the H_3 receptor and useful for maintaining waking-state in the daytime for people with narcolepsy.[14,15] Imidazole containing ciproxifan (GSK189254), a novel HA H_3 receptor antagonist, is more than 10,000-fold selective for human H_3 receptors.[16] After oral administration, the drug enhances the release of ACh, noradrenaline, DA in the anterior cingulate cortex, and ACh in the dorsal hippocampus. These actions significantly improve performance of rats in diverse cognition paradigms, suggesting therapeutic potential for the symptomatic treatment of dementia and other cognitive disorders.[17] However, insomnia can be a troublesome side effect.[18]

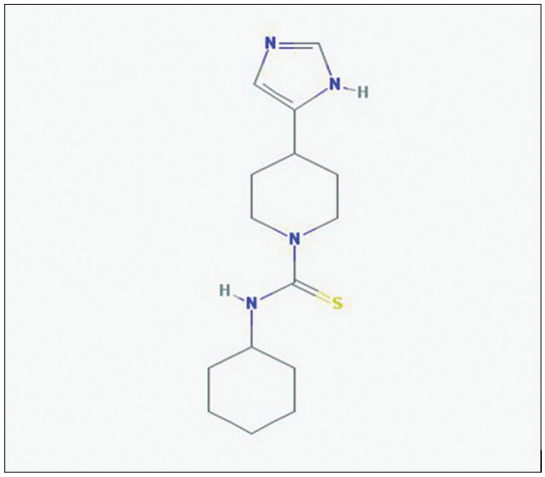

Figure 1: Thioperamide with imidazole ring

General anesthesia is a complex pharmacological response produced by a chemically heterogeneous class of drugs that involves multiple mechanisms, each mediated by pharmacological effects on specific neuronal networks in different regions of the central nervous system [Table 1].

Postoperative Cognitive Dysfunction

The neurodepressive effects of general anesthetics have been presumed to dissipate rapidly with return of cognitive faculties once the anesthetic has been eliminated. Some patients, however, report memory loss and inability to concentrate after general anesthesia, stating that they are "just not the same" after undergoing surgeries several years previously. Symptoms of subtle cognitive decline after surgery are

Table 1: Commonly accepted anesthetic, neurotoxic, and neuroprotective targets of general anesthetics

Target	Anesthesia	Neurotoxicity	Neuroprotection
Synaptic transmission			
GABA receptors	+	+	+
NMDA receptors	+	+	+
Neuronal nicotinic acetylcholine receptors	+	+	
Excitability			
Na+ channels	+	+	+
Ca2+ channels	+	+	+
K+ channels	+	+	+
Intracellular signaling			
Protein kinase pathways	?		+
APP processing		+	+
Tau phosphorylation		+	+

+=targeted, NMDA = N-methyl-D-aspartate APP=Alzheimer precursor protein, GABA=γ-aminobutyric acid, NMDA=N-methyl-D-aspartate

usually described as "postoperative cognitive dysfunction or decline (POCD)." POCD is a distinct entity from postoperative delirium which is characterized by an acute state of confusion with alterations in attention and consciousness. However, there is currently no International Classification of Diseases, Ninth Revision (ICD-9) code for POCD. Cognitive functions include perception, memory, language processing, attention, and abstract thinking. Cognitive dysfunction or decline is present when these processes are affected. Patients often describe their dysfunction as memory loss, lack of concentration, and obtunded abstract thinking.

Incidence of Postoperative Cognitive Dysfunction

Cognitive impairment after major surgery is present in 31%–47% of patients at the time of hospital discharge and in 10% of patients at the end of 3 months.[19] The larger and more invasive operations, such as major vascular surgery, present a larger risk for POCD than minor procedures. Advanced age is a major determinant of POCD, and a prevalence of 6% is reported 3 months after noncardiac surgery in patients above 40 years of age, and 4% in nonsurgical control group. Among the elderly patients, the incidence of POCD 24 h after sevoflurane anesthesia for minor surgery approached 47%. Patients who exhibited POCD at hospital discharge and at 3 months post surgery have a 10% higher incidence of mortality due to patients not adhering to medications/physical therapy regimens or coming for postoperative reviews.[20]

Causal Mechanisms of Postoperative Cognitive Dysfunction

Decreased rates of neurogenesis and synaptogenesis by anesthetic agents can lead to a decline in the total number of neurons and neuronal stem cell function, leading to gradual loss of reserve and increasing the vulnerability of the brain to insults, including exposure to perioperative stressors.[21-23] Every anesthetic agent has the potential to induce apoptosis in neurons secondary to excitotoxicity rather than to the withdrawal of trophic factors.[24]

Residual brain concentrations of isoflurane have been detected 24 h after anesthesia, despite the fact that the volatile agent undergoes minimal biodegradation (<0.2%). The presence of trace levels of isoflurane has a direct effect on neuronal networks to cause postanesthetic memory deficits.[25] Short-term memory involves changes in the strength of preexisting synaptic connections and modulation of existing proteins. Long-term memory requires gene transcription, production of new proteins, restructuring of synapses, and growth of new synaptic connections. Declarative or explicit memory (which refers to memory for facts, objects, places, and events) is particularly vulnerable due to the inhibition of synaptic plasticity in the hippocampus.[26]

Different neuropsychological tests used to measure different domains of cognitive functioning include verbal and language skills, memory and learning, attention, concentration and perception, visual and spatial skills, visual motor and manual skills, numerical skills, executive functions, and composite measures. It is not always possible to dissociate the effects of anesthetics from other factors that impair memory, such as inflammation, analgesic drugs, and concurrent disease. Most anesthetics increase the activity of inhibitory γ-aminobutyric acid subtype A ($GABA^A$) receptors, especially the α5 subunit ($\alpha5GABA^A$) receptors that regulate synaptic plasticity and hippocampus-dependent memory. The $\alpha5GABA^A$ receptors set the threshold for the induction of plasticity in pyramidal neurons by attenuating excitatory input.[27,28] Increased production of amyloid plaque has been observed after daily exposure to halothane or isoflurane. Multiple anesthetic agents can promote hyperphosphorylation of the microtubule-associated protein tau. This leads to self-assembly into neurofibrillary tangles (found abundantly in Alzheimer's disease and Parkinson's disease), especially when associated with hypothermia. Propofol increases tau phosphorylation even if normothermia is maintained. Increase in neurodegenerative markers such as TNF-α, IL-6, and IL-1β after anesthetic exposure is because of neuroinflammation.

Conclusion

H3 antagonists increase the phosphorylation of key intracellular proteins that play a role in the neurodegenerative process. Actions of H3R antagonists/inverse agonists mediated through H3 heteroreceptors enhance the release of various important central NTs in brain such as DA, gamma amino butyric acid, and serotonin, preventing memory impairment and improving anesthesia-associated cognitive deficits.[29] These drugs are expected to become a part of the neuroprotective strategies to minimize the untoward effects of anesthetics. Anesthesiologists should strive to minimize unnecessary exposure to general anesthetic agents and other factors that might potentiate toxicity in susceptible patients. The broad spectrum of activities of H_3R antagonists is expected to find application in preventing and treating POCD with modest and selective effects on cognitive functions in the near future.

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Conflicts of interest

There are no conflicts of interest.

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