How Histamine Can Treat Circadian Rhythm

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ABSTRACT

Circadian dysfunction is an issue for everyone, from intense work schedules and excessive screen time to reversed circadian rhythms in Smith-Magenis syndrome and insomnia in ADHD. Furthermore, newer discoveries suggest that the neurotransmitter histamine takes part in regulating circadian rhythms, and its abnormalities consistently arise in circadian related cognitive disorders. This paper will delve into the complex connections between circadian rhythm and histamine to suggest innovative methods for enhancing both physical and mental well-being.

INTRODUCTION

What is Circadian Rhythm?

Sleep is essential for the functions that keep us alive, like brain performance, preventing diseases, and health in general. Sleep is part of a circadian rhythm, or biological clock, that causes physical and mental changes within a 24-hour cycle. For example, most humans are awake during the day and sleep at night. This clock also impacts digestion, body temperature, and hormone release. Often, irregular sleep is the first sign of a disorder. Changes in our circadian rhythm can lead to health risks such as diabetes, obesity, depression, and sleep disorders (Suni et al., 2023).

What is Histamine?

Histamine is an organic amine neurotransmitter, which are chemical messengers that carry signals from one neuron to another, directing all bodily functions (Hyman, 2005). Histamine is most commonly recognized outside of the brain and spinal cord - regulating allergies, inflammation, infection, and the immune system. However, histamine participates in lesser-known functions that maintain cognitive and circadian wellbeing. From the brain, this neurotransmitter communicates with the entire body. Medications that inhibit or facilitate histamine release can enhance behaviors like cognition and memory as well as decrease the symptoms of various neurological disorders like ADHD and narcolepsy (Haas et al., 2008).

Histamine can have a variety of impacts on the circadian rhythm, and exploring this relationship may provide numerous potential benefits. Here, we will take a look at histamine and its interactions with circadian rhythm and behavior, as well as histamine medications that treat circadian dysfunction.

1. CIRCADIAN RHYTHM

How is Circadian Rhythms Regulated in the Body?

Circadian rhythms regulate almost every physiological process in the human brain and body. A specific region within the hypothalamus called the suprachiasmatic nucleus (SCN) is known for maintaining the biological clock through neuronal and hormonal signals by interpreting light signals (Figure 1). For example, the absence of light tells the SCN to trigger melatonin release, which relaxes the body. Every individual's clock is unique in its 24-hour cycle due to genetic variability, environmental factors, and age. For example, the time we sleep starts later as we shift to adolescence and gradually earlier as we reach old age. This may be due to a natural decrease in SCN activity or a weakening of circadian rhythms with age (Logan et al., 2018).

A typical sleep cycle is around 90 minutes long with two stages: rapid eye movement (REM) and non-rapid eye movement (NREM). REM sleep is when we have vivid dreams and is thought to be important in memory consolidation, cognitive development, and strengthening neural connections in the brain (Peever & Fuller, 2017). It has been proven that a lack of REM sleep decreases the establishment of emotional memories and mood when awake (Glosemeyer et al., 2020). NREM sleep includes all sleep stages, from the lightest to the deepest. In these stages, the body builds bones, repairs muscles, and regenerates tissues (Cherry, 2022).

What is the Impact of Circadian Dysfunction?

Circadian disruption is a key factor in many disorders. Workers who have constantly changing schedules or work the night shift are more susceptible to cognitive issues like depression. Women working night shifts give birth to babies with abnormal weights, preterm deliveries, and miscarriages (Logan et al., 2018). Lack of sleep correlates with inattentiveness, frustration, and hyperactivity in children ages 2–5 (Logan et al., 2018). Around this age, a less healthy circadian rhythm predicts cognitive defects, hyperactivity, and impulsivity when they are older. However, more longitudinal research is needed regarding predictive behavioral problems to give more credit to irregular sleep-wake cycles (Logan et al., 2018).

We do not know whether circadian rhythm dysfunction is the primary cause of neurodegenerative disorders, but dysfunction certainly worsens their progression (Logan et al., 2018). Understanding how histamine affects the circadian rhythm can provide strategies to alleviate neurological dysfunction.

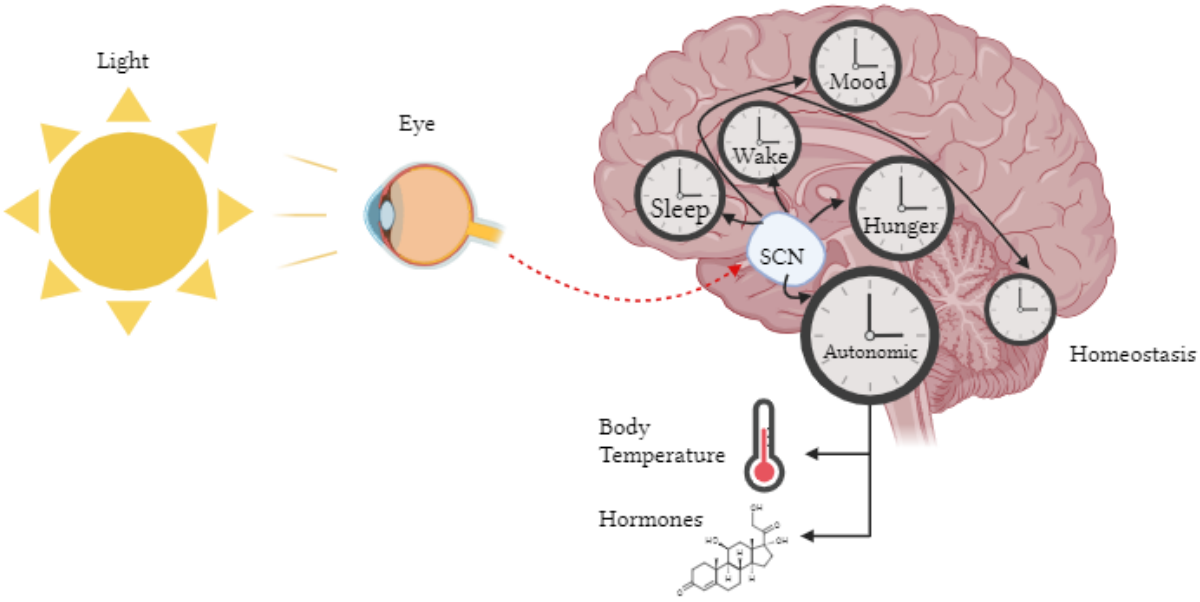

Figure 1. CIRCADIAN RHYTHM REGULATION IN THE BRAIN. The processes that regulate our circadian rhythms include maintaining homeostasis in all of our organs, and managing body temperature and hormone production. Circadian rhythm also regulates thermogenesis, immune function, metabolism, reproduction, and stem cell development (Logan et al., 2018). (This image was created using BioRender.com).

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2. HISTAMINE

What is Histamine's Role in the Body?

Histamine is produced in a wide network of amino acid fibers throughout the body. Histamine receptors facilitate the neurotransmitter's effects on other neurons around the body. It is released when the body detects an irregularity, such as infections or diseases, thereby protecting the body and delivering nutrients to weakened parts. Histamine can also be released in response to contact with pollen or animal dandruff, which can cause allergic reactions. Moreover, recent discoveries suggest histamine release in the brain is involved in many functions through the central nervous system and within the pathology of many neurodegenerative and cognitive disorders. The neurotransmitter's dysfunction has been implicated in many disorders like narcolepsy, depression, Alzeihmer's disease, Parkinson's disease, and disorders related to circadian dysfunction (Haas et al., 2008).

How does Histamine Function through the Brain?

Tuberomammillary Nucleus

The tuberomammillary nucleus (TMN) is located near the back of the brain and is the singular source of histamine in the central nervous system. Other parts of the hypothalamus and brain send signals to the TMN, directing histamine neuron behavior-state activity, and the TMN directs histamine all throughout the body and central nervous system (Chiba et al., 2012).

In the TMN, there are multiple different responses to stress (Chiba et al., 2012). Metabolic stress and chronic restraint stress, which cause anxiety and depression-like behaviors, activate histaminergic neuron release in the TMN (Chiba et al., 2012). In addition, different types of stress activate specific groups of histaminergic neurons. After rats have been restrained, electrically shocked, or have lower blood sugar, different parts of the TMN activate the histamine neurons (Passani et al., 2011).

Here, we review some studies on mice that are significant because rodent genomes are very similar to humans. As a result, many of the diseases, disorders, anatomy, and physiology are similar in both species (Bryda, 2013). The ability to study mice in a controlled setting allows researchers to look at these complicated biological systems, including sleep regulation and histaminergic processes. Rodent research also allows for the testing of prospective medications, which is useful for creating human remedies for ailments associated with circadian dysfunction.

Histamine is produced in TMN neurons, with histidine decarboxylase playing an essential role. By decreasing this enzyme, researchers explored how histamine depletion impacts a variety of mouse behaviors. The researchers first induced chronic brain histamine deficiency in eight-week-old mice, then performed behavior experiments testing locomotive function, memory, social interaction, and sleep while measuring histamine concentration in the hypothalamus and cerebellum. They found that the mice took a longer time solving mazes, displaying symptoms of lower locomotive action and impaired memory. The tested mice also did not try to escape as much as the control mice in the tail suspension test during its final minutes, which was correlated with depression-like behavior. There were no effects on nutritional intake or social interactions. These results suggest that histamine depletion is correlated with decreased wakefulness, an increase in NREM sleep, and less activity overall (Yamada et al., 2020). These results support the notion that histamine plays a role in complex behaviors.

Preoptic Area

The preoptic area (POA) is a structure near the front of the hypothalamus that regulates sleep and body temperature. This area shows sleep-related neuronal activity during the REM and NREM stages of sleep. Sleep-activated neurons from the POA signal project to histamine neurons in the TMN. Histamine indirectly restricts the POA's sleep neurons and coordinates

body temperature, which is useful in response to fever. The large amount of histamine in the POA further suggests histamine's importance in sleep (Rothhaas et al., 2021).

The body's main source of histamine is the brain, which responds to stressors and regulates the activity and behavior of histaminergic neurons throughout. Analyzing this pathology's control of behaviors, sleep regulation, and emotional states facilitates the development of treatments that target these functions.

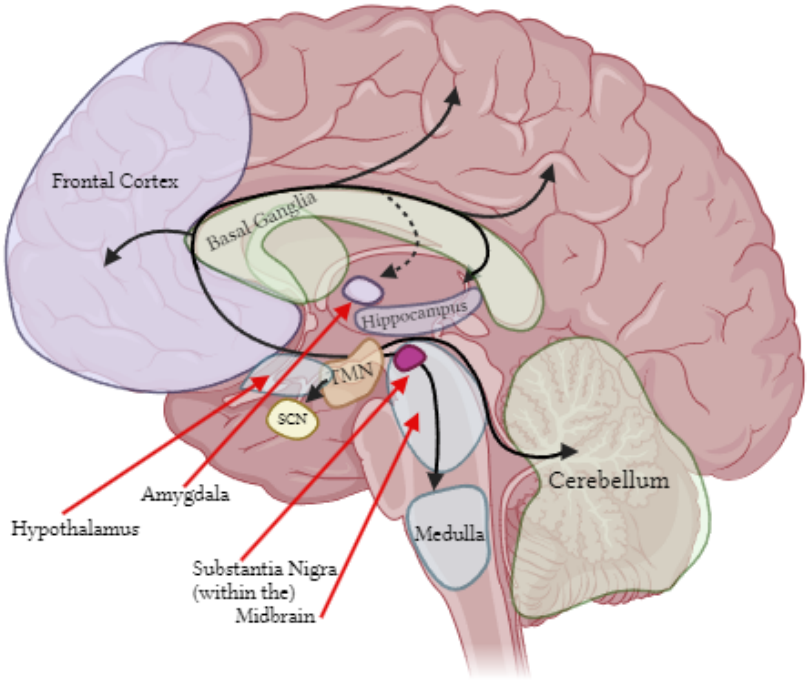

Figure 2. HISTAMINE PATHWAYS IN THE BRAIN. The black arrows display how histamine travels within the frontal cortex, basal ganglia, cerebellum, and hippocampus, which all play a role in memory and learning. Histamine also travels to the amygdala, which controls emotion, and the medulla, which regulates breathing and the heartbeat. The area called the substantia nigra (within the midbrain) is significant when discussing Parkinson's disease. (This image was created using BioRender.com).

How do Histamine Receptors Control Neurotransmitter Communication?

Neurons are the building blocks of the nervous system, which carries messages to and from the body and controls all functions. Between each neuron is the synaptic gap, where nerve cells communicate through neurotransmitters. As these neurotransmitters activate receptors on the other side of the synapse, chemical and voltage charges are sent through the neuron. Molecules close on site receptors which are made up of proteins in the receiving neuron. Neurons sending and receiving information from around the body are what control all brain functions, from thinking to moving (Kandel et al., 2014).

Once neurotransmitters send a message, some can get reabsorbed by the sending neuron. Agonists activate neurotransmitters' receptors. For example, histamine agonists bind to and intensify receptor function like elevating histamine release. Antagonists suppress the effect, blocking receptors and often neurotransmitter production. Neurotransmitter agonists and antagonists make up the medication we take because they control molecule release to produce desired effects (Myers, D. A.,2018).

There are four histaminergic receptors. H1R, H2R, and H3R all play major roles in the brain (Table 1). Not much has been discovered about histamine's fourth receptor, H4R, and its relation to the circadian rhythm (Haas et al., 2008). All receptors are G-protein coupled receptors. This means that after a histamine molecule binds to the receptor, an intermediate G-protein is activated, which enables connections to final destinations or secondary messengers all across the body, allowing for more widespread communication (Kandel et al., 2014). In other words, activation of these receptors starts signaling the activated neuron, which can change how the cell is able to fire and respond to other inputs. GPCRs have different types that impact cells differently, some enhancing and some suppressing.

Understanding the intricate interactions between neurotransmitters is essential for the development of medications that are able to precisely target receptors. Through these neural connections, medications can control histaminergic reactions and neurotransmitter release.

Receptor	Location	Function	Dysfunction	Medication
H1R	All throughout body and nervous system, mass concentrations in brain	Neuroendocrine, behavioral, and nutritional state control (novelty and arousal) *Pathophysiology: memory, eating, metabolism, autonomic functions, sleep disorders, mood, and addiction	Decreased levels noticed in cognitive disorders such as Alzheimer's disease, schizophrenia, and depression	Antagonists treat allergy symptoms (overexposure to sedative effects can lead to cognitive or motor performance setbacks)
H2R	Brain: amygdala, hippocampus, basal ganglia, and cortex	Learning and memory consolidation	Memory and immune function impairment, noticed in schizophrenia	Antagonists treat gastric disorders; in some antidepressants and schizophrenic treatments
H3R	Central nervous system	Cognition, emotion, learning, and memory Pathophysiology: sleep disorders, mood, memory, eating, and addiction	Loss of function relates to sleep, movement, and behavioral disorders, increased severity of neuroinflammatory disease, hyperphagia (extreme hunger), obesity; and increased insulin and leptin levels	Medications target H3R for many neurological disorders

Table 1. RECEPTOR LOCATION, FUNCTION, DYSFUNCTION AND MEDICATION. (Haas et al., 2008)
*Pathophysiology: study of abnormal changes in body functions that are the causes or consequences of a disease (Witthöft, 2023).

3. ANTIHISTAMINES

What are Medications that Treat Disproportionate Histamine Release?

When an allergen enters the body, histamine disproportionately reacts, causing allergic reactions like coughing, sneezing, etc (Sebastian, 2022). Antihistamines treat these symptoms by blocking histamine from overreacting. There are two main types of antihistamines: H1R and H2R antagonists. H1R antagonists treat allergy symptoms. H2R antagonists treat gastrointestinal symptoms like motion sickness, nausea, and vomiting (Sebastian, 2022). Some medications with these properties include (famotidine) Pepcid® and (ranitidine) Zantac®.

H1R Antihistamines

H1R antihistamines work on receptors in the brain and spinal cord and can cause drowsiness (Sebastian, 2022). Through blocking this neuronal histamine production that promotes alertness and wakefulness, antihistamines affect the circadian rhythm by causing sedative effects (Figure 3). Some examples are (diphenhydramine) Benadryl®, (hydroxyzine) Vistaril®, and (doxylamine) Tylenol®. Newer (since the 1980s) antihistamines do not cause drowsiness to the extent that older ones did. These include (loratadine) Claritin®, (cetirizine) Zyrtec®, and (fexofenadine) Allegra® (Sebastian, 2022). An antihistamine called Hydroxyzine is an oral medication that treats anxiety and tension and can aid in sleep disruption, vomiting, and allergies. This antagonist prevents the effects of histamine and can be given before surgery to induce sleep or control anxiety (Kiningham, 2007). Common side effects include drowsiness, blurred vision, dizziness, headaches, tiredness, coughing, and rapid heart rates (Sebastian, 2022). Induced drowsiness can also weaken reaction speed, coordination, and judgment. Some antihistamines may correlate with depression symptoms. A small study of 92 patients who received hydroxyzine and cetirizine for chronic itchiness noticed increased depression and anxiety. However, studies are still being done to further understand this relationship (Özdemir et al., 2014).

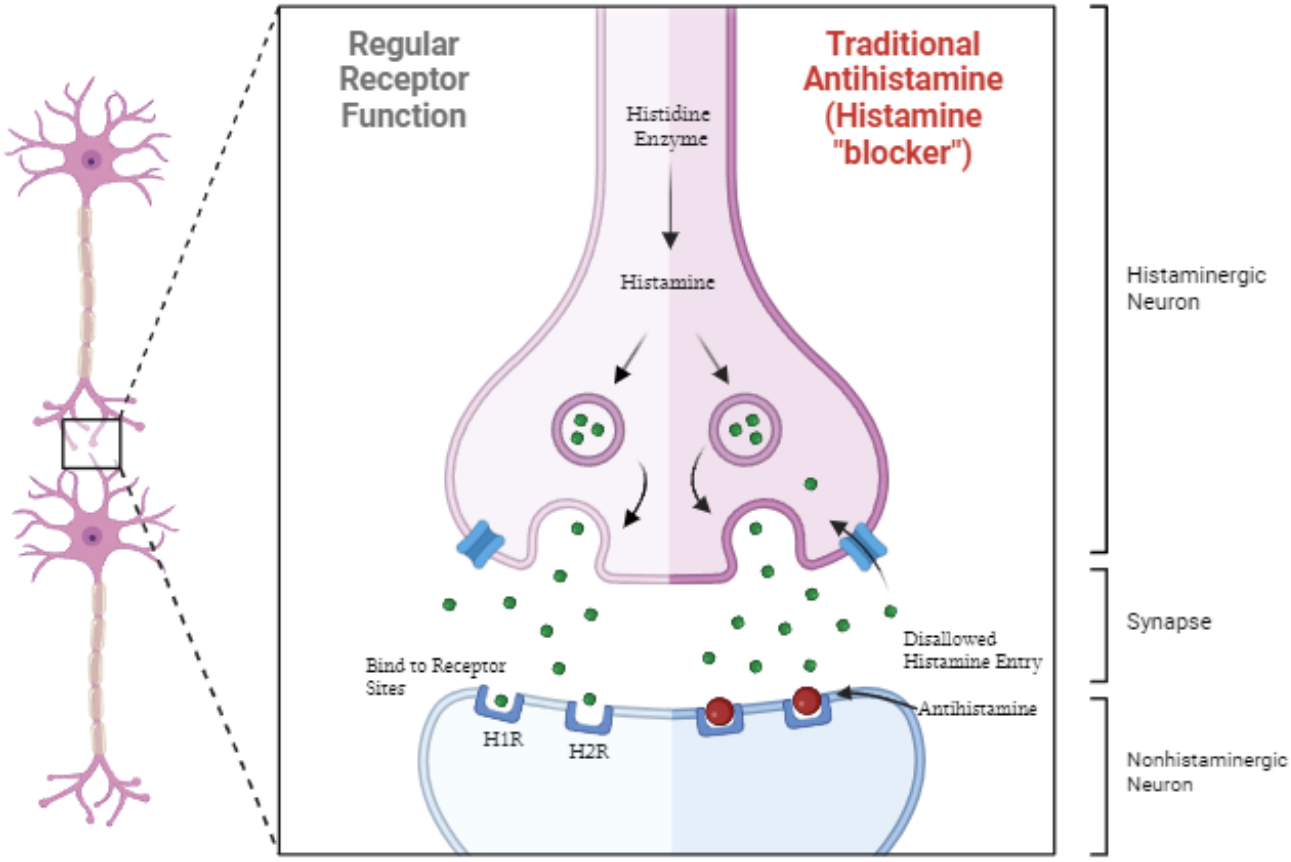

Figure 3. ANTIHISTAMINE: RECEPTOR AND REUPTAKE FUNCTION. This diagram displays traditional antihistamine function. The left, lighter colored side of the neuron shows how histamine typically travels. The right receptor shows how antihistamines block histamines from entering the postsynaptic neuron, which depletes histamine efficacy. (This image was created using BioRender.com)

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4. NOVEL TREATMENTS

How can H3R be used as a Drug Target?

There are no specific neurological disorders that are directly related to histamine depletion or dysfunction, but H3R is a promising target for neurodegenerative disorder medication.

H3R is an autoreceptor, meaning it decreases the chance that a neurotransmitter will be released (Austin, 2018). It can be understood in this manner: H3R pushes the gas pedal of a car

less hard instead of pressing the brakes (Figure 4). H3R also regulates the release of many other neurotransmitters in the body.

H3R antagonists greatly boost the brain waves that optimize attention, alertness, and learning. They press the gas pedal as hard as possible (Figure 4). This proves the ability of medication to treat a multitude of neurodegenerative and cognitive disorders. There are H3R antagonists in development for the potential treatment of schizophrenia and cognitive impairments ranging from Alzheimer's to Parkinson's disease (Passani et al., 2011). One H3R antagonist medication is Pitolisant, a treatment for narcolepsy and Parkinson's that increases histamine by binding to H3R autoreceptors and activating wake-promoting neurons (Harwell et al., 2020). An antagonist known as D177 weakened autistic behaviors and enhanced memory in mice (Eissa et al., 2018). This shows that H3R antagonists have therapeutic potential for treating neurological diseases.

H3R antagonists are intriguing options for drug development as they offer substantial therapeutic promise for treating a variety of neurodegenerative illnesses by regulating histamine release.

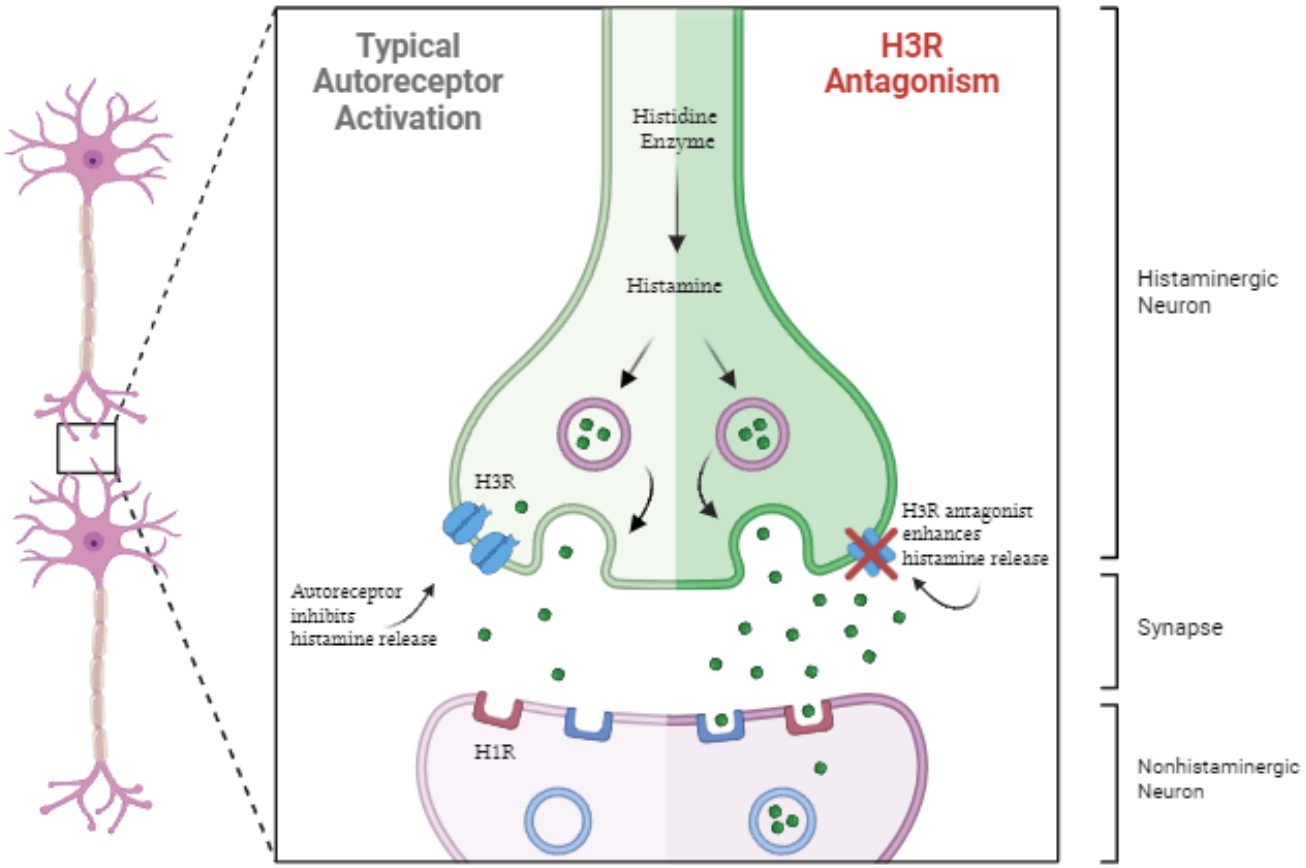

Figure 4. H3R AUTORECEPTOR VS. ANTAGONIST FUNCTION. This diagram displays a neuron, with the left, lighter-shaded side representing a typical histaminergic autoreceptor and the right, darker-shaded side showing a H3R antagonism. The autoreceptor mechanism is as follows: Released histamine will travel to the postsynaptic receptor and bind to the autoreceptor, which inhibits histamine release. Non-histaminergic receptors that receive histamine from H3R autoreceptors include serotonin, dopamine, acetylcholine, and GABA. In a potential medication, an H3R antagonist blocks the autoreceptor, disallowing histamine to return to the presynaptic neuron, meaning more histamine releases. This can enhance cognition, learning, and memory. (This image was created using BioRender.com).

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5. EMERGING PRINCIPLES

How can Histamine Treat Circadian Rhythm Dysfunction?

We have discussed how histamine medication is useful for more than just allergies or infections. Histaminergic activity shows a clear circadian rhythm, with high levels during the day and low levels during sleep. This is the activation of histaminergic neurons in the brain's cortex that drive

arousal while restraining neurons that promote sleep (Haas et al., 2008). We can use this to our advantage when discussing potential treatments.

Narcolepsy

Narcolepsy means having a sharp attack of falling asleep, at times triggered by a strong emotion like laughter or anger (Myers, D. A.,2018). This is caused by the lack of a sleep neurotransmitter called orexin, but it can also be due to gene variations, hormonal imbalances, or sudden shifts in sleep-wake patterns (Thannickal et al., 2000). Those with narcolepsy are usually tired throughout the day, experiencing irregular and disrupted sleep. Researchers discovered that the brains of patients with narcolepsy contained 94% more histaminergic neurons than non-narcoleptic ones (Valko et al., 2013). One theory is that cells can produce histamine but cannot release enough to properly promote wakefulness (Huang et al., 2001). Modafinil is a medication primarily used to activate dopamine neurons that fight narcolepsy and Parkinson's disease, but it also activates histaminergic neurons, promoting alertness (Passani et al., 2011).

Parkinson's Disease (PD)

PD is a neurodegenerative disorder that greatly affects locomotive function. One study explored the relationship between PD and circadian rhythm. Results displayed that lower circadian rhythms were associated with a higher risk of incident PD, suggesting circadian-based intervention might slow disease progression (Nassan et al., 2021). In another study, chronic circadian disruption in a toxin-induced rodent model of PD revealed magnified motor deficits by provoking the degeneration of neurons (Nassan et al., 2021). Symptoms of PD commonly include circadian defects like abnormal sleep-wake cycles, cognitive impairment, and sensory deficits.

In Parkinson's disease, there is a decrease in histamine transport capacity in the substantia nigra, which is located in the midbrain and helps control movements. Terminal fibers that contain histamine grow around other neurotransmitter neurons, signaling damage to wake-promoting neurons (Haas et al., 2008). In addition, H3R binding is abnormally high in the parkinsonian substantia nigra within the basal ganglia, and low in people without PD (Haas et al., 2008).
Histamine dysfunction clearly relates to less-robust circadian rhythms. As well as the H3R antagonists listed previously, H1R antagonists improve these motor and cognitive functions. One antihistamine called diphenhydramine (which is common in medications like Benadryl for reducing allergic symptoms) can decrease stiffness and tremor symptoms (Sicari, 2023).

PD not only impacts movement but also demonstrates circadian irregularities, which correlates with atypical histamine receptor function. Antihistamines and H3R antagonists are able to treat neurological and motor dysfunction alike.

Insomnia

Insomnia is a common symptom of many neurological disorders. Having insomnia means having persistent problems falling or staying asleep. A potential cause is an irregular light-dark cycle or sleep-wake patterns that are correlated with histaminergic receptors (Schwab, 2023). When genetically deprived of H1R, mice have a disrupted circadian rhythm displayed in their sleep patterns. H1R agonists raise time awake as histamine naturally inhibits sleep focused neurons (Passani et al., 2011). A study evaluated sleep latency, total time asleep, number of sleep disturbances, and subjective sleep efficiency with H1 receptor antagonist treatment. Low doses of a medication called doxepin, with powerful H1 and H2 antihistamine activity, provided consistent sleep benefits. Other H1R antagonists show mixed results. For now, antihistamines should only be taken after primary insomnia treatments fail, as tolerance is easily built, and be continuously tested to prevent harm (Griend, 2012).

Prader-Willi Syndrome (PWS)

Prader-Willi syndrome is caused by the loss of imprinted genes on chromosome 15 that affect infants' health and can lead to obesity, intellectual impairment, and obsessive-compulsive disorder (OCD) (Butler, 2011). Other common symptoms are sleeping for shorter periods of time and heavy tiredness during the day (Logan et al., 2018).

Typical psychotropic medications used to manage behavioral disturbances are usually very weak and increase the risk of drug-associated adverse effects. Novel treatments are needed to ease the symptoms of PWS. One way is Pitolisant, the H3R antagonist previously discussed for treating narcolepsy. A case study was done on a 15-year-old girl with PWS, OCD, autism, mild intellectual disability, hypothyroidism, and scoliosis whose previous medications failed to reduce circadian dysfunction symptoms of restlessness, irritability, and behavioral outbursts. After 10 days of Pitolisant along with her current psychotropic medications, she was able to complete academic tasks with more ease and needed less help to complete jobs at home, something she had not been able to do for years. An increased dose months later found improved muscle tone, faster walking, less sleepiness in the daytime, and fewer behavioral outbursts - all circadian rhythm enhancements. Continued increasing found improved critical thinking skills and frustration levels, although these symptoms still existed. Increased Pitolisant with decreased or discontinued medications reported better sleep, attention, and behavior. Some adverse effects, like small weight gain and more sweating, were noted; however this also may be due to puberty (Pennington et al. 2021).

PWS produces notable circadian dysfunction, including tiredness and behavioral outbursts. Conventional medication may not always provide effective relief, so H3R antagonists, such as Pitolisant, can be used to regulate circadian rhythm and mitigate negative symptoms.

Smith-Magenis Syndrome

Smith-Magenis syndrome causes skeletal and facial abnormalities, which also lead to obesity, intellectual impairment, eating and digesting issues, as well as circadian impairments. Extreme cases cause a complete reversal of the original circadian rhythm and sleep-wake patterns (Logan et al., 2018). Antihistamines like diphenhydramine can manage sleep problems in children with SMS (Rinaldi et al., 2021). Trazodone is a medication that is used to mainly treat depression. However, its moderate antihistamine components can treat daytime sleepiness in SMS and insomnia. Trazodone decreases sleep latency, increases sleep duration, and improves daytime functioning (Kaplan 2020).

SMS has circadian impairment, which includes feeding irregularities and disrupted sleep-wake cycles. Antihistamines can regulate circadian rhythm by inducing drowsiness.

Depression

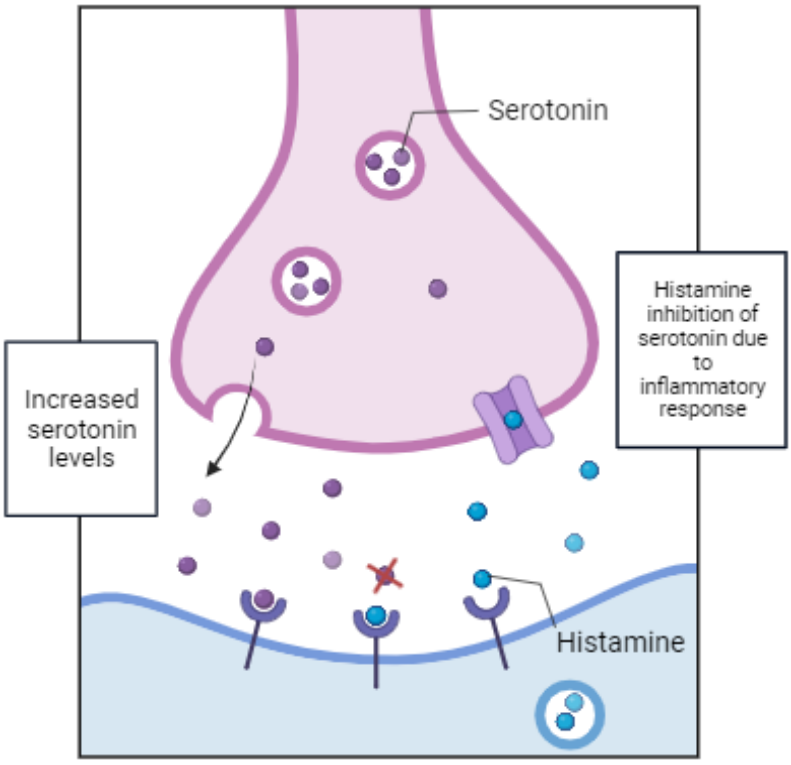
Depression affects 1 in 10 adults in the United States. Many individuals do not respond to pharmaceutical antidepressant therapy, which is why it is imperative to find other, novel treatments (Glick, 2021). A potential reason why circadian dysfunction is highly correlated with depression is because disruption affects neuronal growth during the teenage years (Logan et al., 2018). A delayed biological clock (SCN) during the teenage and young adult years causes sleep disturbance, decreased hormone production, and an abnormally increased core temperature. Up to 90% of depressed patients have trouble sleeping, with increased amounts of REM sleep but decreased NREM deep sleep. Because of this, a distinguishing factor for depression is this REM abnormality (Germain, 2008). Also, histamine depletion produces observable characteristics that model depression, as histaminergic neurons respond to signals that are related to depression symptoms (Haas et al., 2008).

The more commonly researched neurotransmitter in regards to depression is serotonin, also known as the happy chemical. High levels of serotonin are linked to mood improvement, and low levels relate to depressive symptoms. In a study, researchers placed microelectrodes (to analyze molecular data) into mice's hippocampus and injected inflammation through a toxin. The inflammation caused drastic decreases in serotonin (Figure 5). This explains why SSRI drugs like Escitalopram can be limited in their ability to improve emotional health; they cause inflammation by preventing histamine reuptake, which keeps histamine levels high. When nontraditional antihistamines (traditional antihistamines do not affect SSRIs) were used to lower histamine levels, the drug was able to work properly. Histamine can directly inhibit serotonin release once the inflammatory response is provoked. In humans, there is significant research

proving patients with depression and severe inflammation are most likely to not respond to antidepressants. Moreover, researchers from the University of Florence, Italy, tested mice's brains and discovered the SSRI drugs Citalopram and Paroxetine do not work in mice that cannot produce histamine. This research concludes that histamine and inflammation play a large role in the pathology of depression (Glick, 2021).

Histamine depletion is associated with depression-like symptoms, and its interactions with serotonin influence mood. With SSRI depression medications, inflammation hinders serotonin function, emphasizing histamine's critical involvement in depression pathogenesis.

Figure 5. HISTAMINE INHIBITS SEROTONIN PRODUCTION. This diagram displays increased serotonin levels due to SSRI drugs that treat depression. Histamine levels also increase, causing more inflammation and inhibiting serotonin release. (This image was created using BioRender.com).



Attention Deficit Hyperactivity Disorder (ADHD)

ADHD negatively impacts brain development with symptoms such as inattentiveness and impulsivity. Those with ADHD commonly have sleep issues because of circadian rhythm delays (Logan et al., 2018). Some 75% of adults with childhood-onset ADHD have a delayed circadian rhythm phase, with sleep-related movements occurring around 90 minutes later than non-ADHD adults, altered core body temperatures, and hormone production delays (Lunsford et al., 2018). Additionally, there have been recent studies on histamine and ADHD by Dr. Hilario Blasco-Fontecilla presented at the National Congress of the Spanish Association of Child and Adolescent Psychiatry in Madrid. This team studied the DAO enzyme found in many foods that

helps break down extra histamine to alleviate unwanted symptoms. With this enzyme deficiency, histamine is not able to break down effectively and goes to the bloodstream, which correlates to many allergic and respiratory symptoms (Duelo, 2022).

Another successful treatment for ADHD is ABT-239, a new, exceptionally effective H3R antagonist that targets the H3R to increase histamine release from the TMN among other brain areas. It has experimentally been able to reduce seizures, head bobbing, and immobility in mice. A medical combination with ABT-239 can turn a short-term memory into a long-term one, not including histamine-depleted mice. Administration improved the performance of rat pups that exhibit behavioral features of ADHD including hyperactivity, inattention, and impulsivity (Provensi et al., 2016).

Histamine's pathology in ADHD is underlined through prolonged circadian rhythms, as enzyme deficits cause histamine-related symptoms. H3R antagonists promise moderation of these ADHD behaviors.

Schizophrenia

Schizophrenia is a mental illness that can lead to delusions, hallucinations, disorganized speech, and a lack of motivation (Myers, D. A.,2018). There is no cure, which is why treatments must be continuously advanced to provide further relief. On average, schizophrenic patients take longer to fall asleep, wake up later, and often have broken, irregular sleep episodes, and their biological clocks are usually longer than the regular 24-hour day. This dysfunction diminishes cognition and worsens quality of life, corresponding to obesity, metabolic diseases, social withdrawal, and overall earlier mortality. Light interventions that can be applied without affecting daily life regulate the circadian clock and help these patients sleep longer. It is important to note that another hypothesis regarding the advanced 24-hour clock can correlate to less light exposure (Skeldon et al., 2021).

H1R expression decreases in the frontal cortex, suggesting increased histamine release may impact schizophrenia where there are other anatomical differences in the frontal cortex. This is also seen with elevated levels of a histaminergic compound (Haas et al., 2008). There are many promising trials that are being executed on humans, like the H3R antagonist ABT-288, which treats schizophrenia cognitive impairment symptoms.

Linked to histamine malfunction, irregular sleep-wake patterns are highlighted in schizophrenia. Continuing studies are researching H3R antagonists in an attempt to treat these neurological impairments.

Disorder	(Potential) Cause	Circadian Dysfunction/Symptoms	Histamine Treatment
Insomnia	Irregular light-dark cycle or sleep-wake patterns	Unable to fall/stay asleep	H1R antagonists (like Doxepin) - only used when traditional insomnia treatments fail
Narcolepsy	Lack of neurotransmitter orexin, genetics, hormones, and sudden sleep-wake patterns shift	Sharp attacks of falling asleep, triggered by a strong emotion	Pitolisant, Modafinil activates histaminergic neurons, promoting alertness
Parkinson's Disease	Degeneration of dopaminergic neurons	Movement loss, tremors, abnormal sleep-wake cycles, excessive sleepiness, cognitive impairment, sensory deficits	Diphenhydramine decreases stiffness and tremors, Pitolisant, Modafinil
Prader-Willi Syndrome	Genetic disorder: Developmental issues with chromosome 15	Obesity, intellectual impairment, OCD, heavy tiredness, less sleep	Pitolisant
Smith-Magenis Syndrome	Genetic disorder Deletion of gene on chromosome 17	Skeletal and facial abnormalities, and eating, intellectual, and circadian impairments (circadian rhythm reversal)	Diphenhydramine, Trazodone
Depression*	Brain chemical imbalance	Sleep disturbance, hormonal production decrease, abnormally increased core temperature	Certain antihistamines, such as hydroxyzine
Attention Deficit Hyperactivity Disorder*	Unknown: genetics/environmental factors	Inattentiveness, impulsivity, circadian rhythm delays, altered core body temperatures, hormonal production delays	ABT-239 H3R antagonist (mice)

Table 2. HISTAMINE TREATMENT OF NEUROLOGICAL DISORDER CIRCADIAN DYSFUNCTION. This table is a summary of all discussed in this section.

6. CONCLUSION

In this paper, we explored the relationship between two seemingly distant but interconnected topics - histamine and the biological clock - to propose novel approaches for improving physical and mental conditions. The relationship between circadian and histamine dysfunction can help us understand how to provide symptom relief for many disorders, from depression to Parkinson's disease. Looking into various experiments allows for discussion of possible therapeutic treatments that target histamine irregularities to maintain circadian function. Addressing modern challenges requires modern solutions. New revelations in the neurotransmitter field may just be the key to improving our well-being.

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