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ENGLISH VERSION

Chinese version is in the back

SMART magazine

DOES THE MONKEY KING'S FIXATION ACTUALLY EXIST? NERVE CELLS FOUND THAT HALT ALL MOVEMENT

SUMMARY

In this study, researchers investigated the distribution and function of Chx10+ neurons in the pontine nucleus (PPN) and the periaqueductal gray matter ventrolateral column of the midbrain (vIPAG). They discovered that Chx10+ neurons in the PPN were unevenly distributed, primarily concentrated in the rostral region. These neurons were found to be predominantly involved in glutamate signaling. Activation of Chx10-PPN neurons induced motor arrest and suspended various motor behaviors in mice, indicating their role in controlling voluntary and controllable movements. Additionally, the study showed that Chx10-PPN neuron activation influenced respiration and heart rate, suggesting their involvement in autonomic regulation. However, the motor arrest patterns induced by Chx10-PPN and Chx10-vIPAG neuron activation were distinct, implying separate neural mechanisms. These findings contribute to our understanding of motor control and its potential relevance to conditions like Parkinson's disease.

VOCABULARY

Pontine nucleus - A group of nuclei located in the pons, which is a part of the brainstem. The pons play a crucial role in various functions, including the relay of signals between different parts of the brain and spinal cord.

Chx10 neurons - A subpopulation of glutamatergic PPN neurons with a rostral bias.

Neurotransmitter Phenotype - Specific neurotransmitter(s) that these neurons produce and release to transmit signals to other neurons or target cells.

Optogenetics - Technique that uses light to control the activity of specific neurons genetically modified to be light-sensitive. In this case, Chx10-PPN neurons were manipulated using light stimulation.

EXPERIMENTAL PROCEDURE

Distribution of Pontine Nucleus Chx10

The scientists tried to explore the distribution of pontine nucleus Chx10 in PPN glutamatergic neurons. First, they crossed Chx10 Cre mice with the R26R tdTomato cell line, which was used to permanently label Chx10+ neurons. The results showed that Chx10+ neurons were unevenly distributed along the rostrocaudal axis of the PPN, mainly on the rostral side.

Neurotransmitter Phenotype of Chx10+

The scientists then investigated the neurotransmitter phenotype of Chx10+ neurons in the PPN. In sections of Chx10 Cre, they performed in situ hybridization for Vglut2 mRNA using RNAscope combined with eYFP immunostaining. All Chx10+ neurons in R26R EYFP reporter mice expressed eYFP and quantified their simultaneous expression of two or more genes. The majority of Chx10+ cells expressed as Vglut2 mRNA (89.67% $\pm$ 0.75%). This indicates that these neurons primarily use glutamate as their neurotransmitter. Glutamate is an excitatory neurotransmitter, meaning it enhances the activity of the neurons it communicates with.

Play a Role in Motor Control?

Optogenetic methods are used to investigate whether Chx10-PPN neurons play a role in motor control. Mice were tested in two different environments: the first was a linear channel used to assess the effect of Chx10-PPN neurons on voluntary movement. This environment likely allowed researchers to observe changes in locomotion and assess how these neurons affect basic motor functions. The second, a cylindrical arena, was used to assess the effect of this neuron on other controllable movements such as grooming or upright walking.

Tests showed that in the first linear channel, the Chx10-PPN neuron was activated unilaterally, which induced a motor arrest and an almost instantaneous recovery at the end of the stimulus. In the second cylindrical arena, activation of Chx10-PPN neurons transiently suspended the mice's walking, grooming, and standing behaviors. These results suggest that the motor arrest in mice is due to the activation of Chx10-PPN neurons.

Activation of Chx10-PPN neurons leads to global motor arrest.

Respiration and Heart Rate Effects

Since PPNs play an important role in autonomic regulation, whether Chx10-PPN activation also has effects beyond limb movement output, so they investigated the effects of this on respiration and heart rate. Using synchronized whole-body volumetric tracing (WBP), wireless electrocardiography (ECG), and other activity tracking, they recorded freely awake mice firing at random intervals to Chx10-PPN neurons using blue or yellow light for the control-delivery of light stimuli.

BENEFITS OF "FIXATION" FOR PEOPLE

Stereotaxic techniques may help researchers gain a better understanding of the symptoms of Parkinson's disease, as well as help to understand the pathogenesis of Parkinson's disease. PPN technology has been used to target deep brain stimulation methods to improve PD symptoms. Successful methods of deep brain stimulation targeting the PPN to alleviate motor dysfunction in Parkinson's disease should consider avoiding the rostral portion of the nucleus to prevent activation of the Chx10 population. "Motor arrest or slowed movement is one of the main symptoms of Parkinson's disease. We hypothesize that in Parkinson's disease, these particular nerve cells in the PPN are over-activated. This inhibits movement." Ole Kiehn concludes, "This study therefore focuses on the basic mechanisms by which the nervous system controls movement and may ultimately help us understand the cause of some of the motor symptoms of Parkinson's disease."

ABSTRACT

The Monkey King has the ability to hold creatures in place without moving, called fixation, and now this skill is about to be realized by scientists! Recently, scientists have discovered a group of neurons in the brains of mice that, when stimulated, cause the mice to stop all movement, including the normal rhythm of breathing. When the stimulation ended, the mice would start moving exactly where they had stopped, minute by minute. Scientists say the study may help to understand some of the mechanisms underlying Parkinson's disease - the main symptom of which is slowed movement.

KEYWORDS

eurons, pontine nucleus, glutamate (PPN), whole body volumetric tracing (WBP), neuraxis, Parkinson's disease (PD), motorized stereotaxic injection system (Stereo Drive Robot Stereotaxic, Neurostar)



INTRODUCTION TO EXPERIMENT

Scientists have made a new discovery that gives us an understanding of what happens in the brain when movement suddenly stops. "We found a group of nerve cells in the midbrain that stop all movement when it is stimulated. Not just everyday behaviors like walking, but even all forms of motor activity. They can cause mice to stop breathing or breathe slowly and slow their heart rate," said Ole Kiehn, a professor in the research program.

"There are multiple ways to stop movement. What's special about these nerve cells is that once activated, they cause movement to pause or freeze. It's like setting a movie to pause. The actor's movements suddenly stop on the spot."

The nerve cells stimulated by the researchers are found in a region of the midbrain called the nucleus Pontis nuclei (PPN), and they are distinct from other nerve cells through specific molecular markers associated with Chx10.

The PPN is common in all vertebrates, including humans. Therefore, even though this study was conducted in rats, the scientists hope that this phenomenon applies to humans as well.

RESULTS/SUMMARY

The results showed that activation of Chx10-PPN neurons caused the mice to pause in their activity and, at the same time, they exhibited respiratory pauses, whereas, during the activity period after the end of activation, the mice's respiration and heart rate very rapidly returned to pre-activation levels. Surprisingly, in the absence of any artificial intervention, the mice also produced similar manifestations of locomotion and arrest. These results confirm that the behavioral patterns observed during activation of Chx10-PPN neurons also persisted in normal times, confirming that there are natural factors influencing the mice.

Activation of glutamatergic neurons in the periaqueductal gray matter ventrolateral column of the midbrain (vIPAG) elicited an overall motor arrest associated with the innate fear response, and a subpopulation of Chx10-expressing glutamatergic neurons in the vIPAG elicited a freezing response as well. So here the scientists went on to explore whether stimulation of Chx10-vIPAG neurons elicits motor arrest similar to Chx10-PPN stimulation.

The results show that in the first linear channel, unilateral photostimulation activation of Chx10-vIPAG neurons is also effective in stopping ongoing movements, but unlike Chx10-PPN activation, the latency of Chx10-vIPAG activation to induce motor arrest is significantly longer than that during Chx10-PPN activation, and after the end of Chx10-vIPAG activation mice motor activity does not return to pre-activation levels. In the second type of circular arena (cylindrical arena), mice were unable to continue previous locomotor steps after the end of Chx10-vIPAG activation. During the monitoring of respiration and heart rate frequencies of mice, it was found that the degree of respiration and heart rate depression induced by Chx10-vIPAG activation was significantly lower than that induced by Chx10-PPN activation. The above results suggest that the overall motor arrest induced by Chx10-PPN is not related to the overall motor arrest induced by Chx10-vIPAG.

In summary, the present study identified a brainstem response induced by the activation of PPN Chx10+ as well as Chx10-vIPAG neurons that resulted in overall motor arrest. Overall motor arrest was accompanied by apnea and decreased heart rate. Given the significance of PPN in the pathogenesis of Parkinson's, this article may be of potential value.

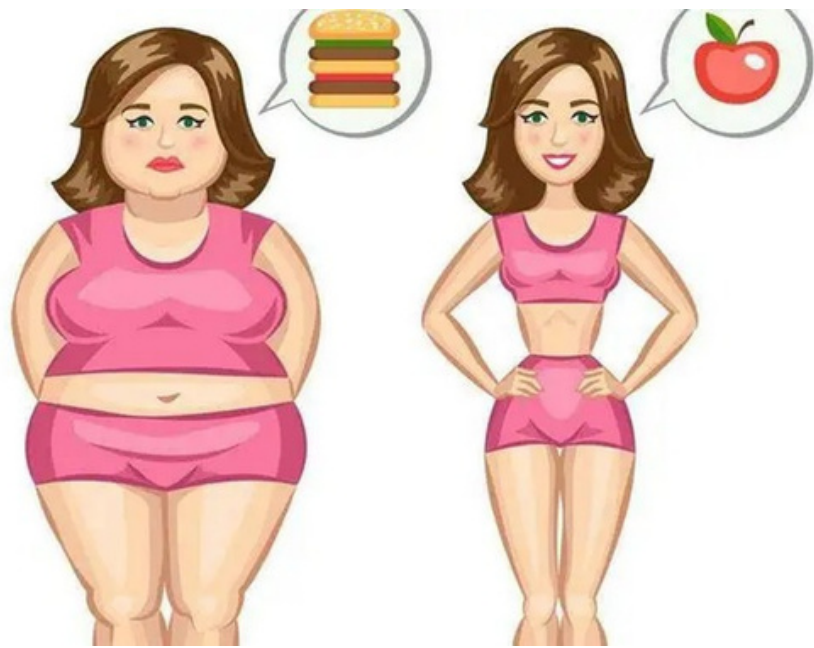
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SIMEGLUTIDE

AUTHOR: ZHIYUAN LI

Keywords: weight loss, weight, diet pills, heart disease, diabetes



Weight is always what most people are concerned about. There are various methods for weight loss such as exercise, diet, and weight loss drugs. There is no doubt that exercise is the most healthy way to lose weight. For the present tense times and lazy people, maybe weight-loss drugs are their first choice.

Amazingly, there appears to be a strong correlation between weight loss drugs and hypoglycemic drugs (drugs used to treat diabetes). Bifidum, Lljing, Luting, and Acarbose can all reduce weight. In August of 2023, Novo Nordisk announced the availability of its product, glipizide, as a hypoglycemic agent that not only has the effect of weight loss but also significantly reduces the probability of adverse cardiovascular events.

Greatly reduces cardiovascular events

Simeglutide is a GLP-1 receptor agonist. As an incretin, it stimulates insulin secretion in a glucose-dependent manner, inhibits glucagon secretion, reduces blood glucose, and slows gastric emptying, thereby suppressing appetite. Because it can reduce weight, it is also believed to reduce the occurrence of cardiovascular events. In this randomized, double-blind, parallel-group, and placebo-controlled phase III trial conducted by Novo Nordisk, Semaglutide 2. 4mg was used as an adjunct to standard therapy to prevent MACE in patients with cardiovascular disease, overweight or obesity, and no history of diabetes over a 5-year period. The trial included 17, 604 adults aged 45 and above who were overweight or obese, had cardiovascular disease, and had no history of diabetes. The primary endpoint was the first occurrence of MACE, including cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke. By the end of the study, only 1270 patients developed MACE. In contrast to placebo, once a week for five consecutive years of subcutaneous injections of 2. 4 mg Semaglutide for SMR-1 can reduce the incidence of MACE by 20 %.

Far away from peers

According to a report by Novo Nordisk, according to the results of the Phase IIIb trial, the weight loss rate of the 2. 4mg dose of Semaglutide injection was 15. 8 % after 68 weeks of treatment (a 70kg patient can lose 58. 94kg after 68 weeks), indicating a significant effect. The advantages of selegiline include not only:

- 1) In 2021, 424 RCT experiments and network meta-analysis showed that among the 9 major categories and 21 hypoglycemic drugs of Smeglutide injection, it showed the best weight loss effect. Other studies have confirmed that Smeglutide also has advantages over the same company's Liraglutide.
- 2) Smegglutide only requires one dose per week, which is more convenient compared to other GLP-1 weight loss pills on the market that require one dose per day.
- 3) He is an FDA-approved hypoglycemic drug that can be used for weight loss.
- 4) Different from other weight-loss drugs, Semaglutide can not only control blood sugar and lose weight but also reduce cardiovascular events compared with other drugs. Therefore, the FDA also approved it for patients with type 2 diabetes combined with cardiovascular disease.

FDA NEWS RELEASE

FDA Approves New Drug Treatment for Chronic Weight Management, First Since 2014

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For Immediate Release: June 04, 2021

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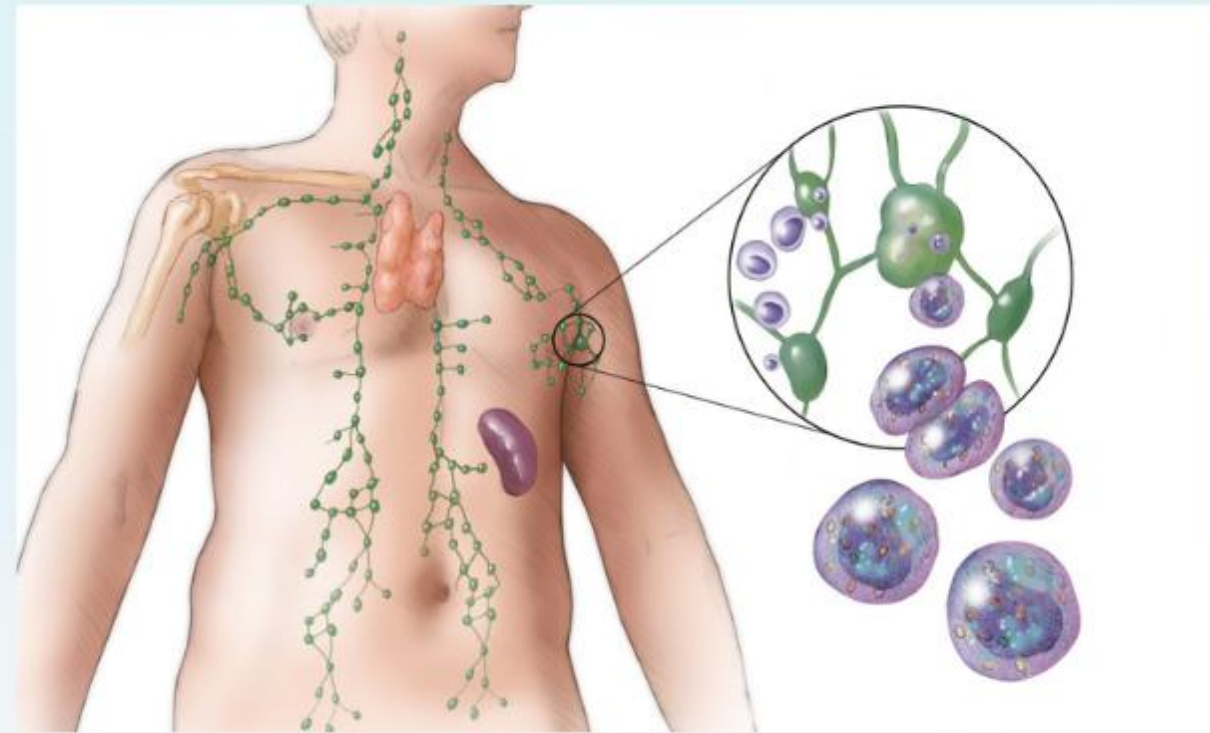
Today, the U.S. Food and Drug Administration approved Wegovy (semaglutide) injection (2.4 mg once weekly) for chronic weight management in adults with obesity or overweight with at least one weight-related condition (such as high blood pressure, type 2 diabetes, or high cholesterol), for use in addition to a reduced calorie diet and increased physical activity. This under-the-skin injection is the first approved drug for chronic weight management in adults with general obesity or overweight since 2014. The drug is indicated for chronic weight management in patients with a body mass index (BMI) of 27 kg/m² or greater who have at least one weight-related ailment or in patients with a BMI of 30 kg/m² or greater.

Although with the development of technology and drugs, there are more and more ways for us to lose weight, according to experimental research, exercise is still the best way to lose weight and control cardiovascular events.

What is lymphoma? Is a tumor that grows in the lymph nodes a lymphoma?

Keywords: lymphoma, cancer, medical breakthrough

The development of lymphoma occurs when one of the white blood cells called lymphocytes grows uncontrollably. The lymphocytes in our body help our immune system fight infections by traveling around in our lymphatic system. The lymphocytes are divided into two types: T lymphocytes (T cells) and B lymphocytes (B cells). With all types of lymphoma, diffuse large B-cell lymphoma (DLBCL) constitutes almost one-third of all clinical cases of non-Hodgkin's lymphoma (NHL). Since its discovery, this type of lymphoma has been labeled "aggressive" or "moderately to highly malignant" lymphoma. Because DLBCL is heterogeneous, it has different subtypes with different clinical characteristics, genetic changes, and treatment responses.



Reference #1 Determining prognosis for patients with diffuse large B-cell lymphoma

Is lymphoma common? What is the rate?

Non-Hodgkin's lymphoma (NHL) is one of the most common cancers worldwide, accounting for approximately 4% of all cancers. Especially in recent years, the incidence rate of lymphoma has shown a more obvious rising trend. According to the China Anti-Cancer Association (CACA), “ the annual incidence of lymphoma in China is about 75,400, with an incidence rate of 4.75/100,000, and the number of deaths is about 40,500, with a mortality rate of 2.64/100,000. ”

The development of DLBCL Treatment

r-CHOP Regimen

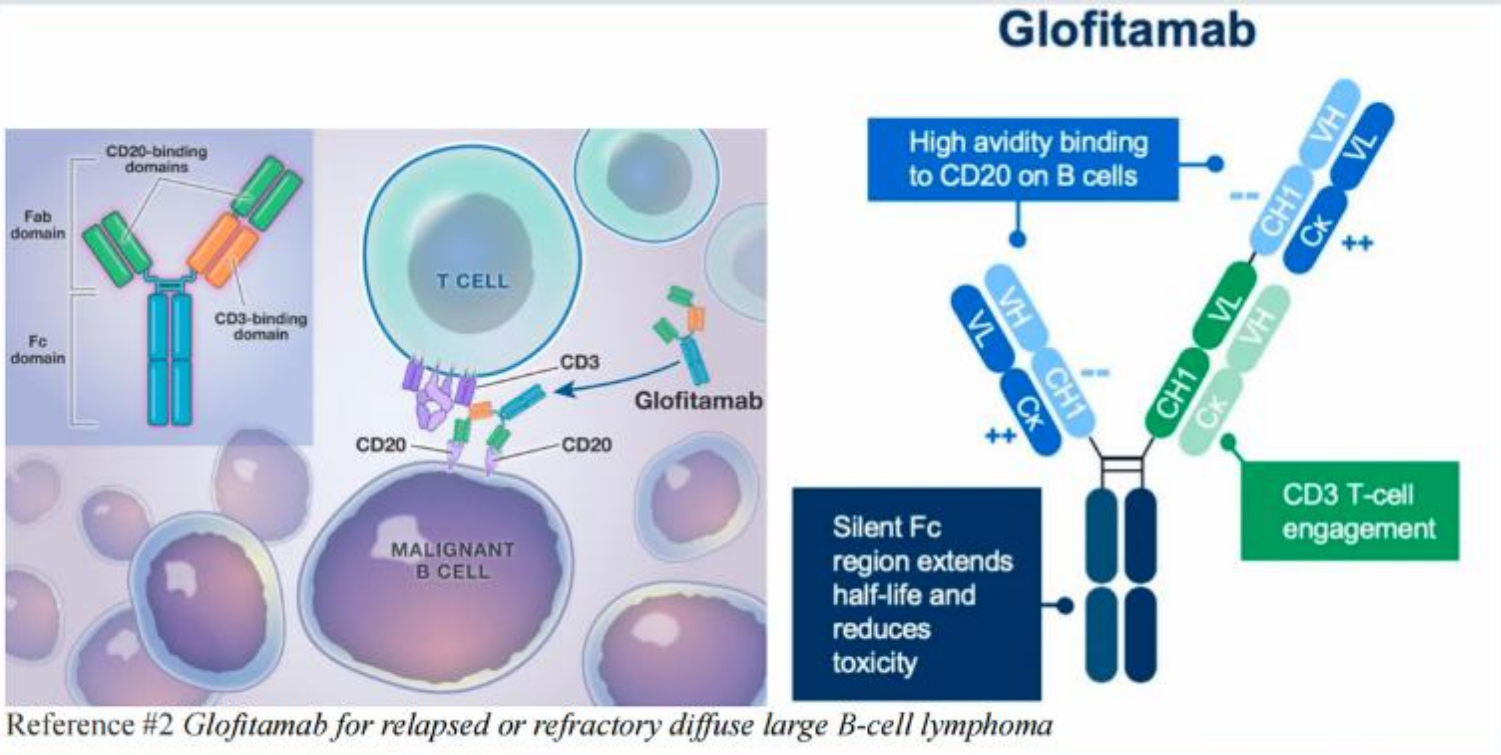
r-CHOP (rituximab + cyclophosphamide + adriamycin + vincristine/vincristine + prednisone) is the current standard of care for the treatment of DLBCL, but resistance and relapse are still a problem for up to 30%-40% of patients.

Stem cell transplantation

DLBCL patients who experience refractory or relapsed results following chemotherapy often undergo stem cell transplantation. In most cases, stem cell transplants are autologous, meaning the patient receives his or her own stem cells prior to the procedure. In other cases, patients will receive an allogeneic transplant in which they receive stem cells from another donor. Similar to r-CHOP Regimen, clinical trials show a high rate of relapsed or refractory large B-cell lymphomas even after finishing treatment.

Glofitamab-gxbm (Columvi, Genentech, Inc.)

On June 15, 2023, the Food and Drug Administration granted accelerated approval to Glofitamab-gxbm (Columvi, Genentech, Inc.) for relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapy. The study showed that patients treated with Columvi had an overall remission rate (the sum of complete and partial remissions) of 56%, with a complete remission rate of 43% and a median duration of remission of 1.5 years. On March 25 of this year, the drug was authorized by Health Canada for conditional use in adult patients with R/R DLBCL (relapsed or refractory diffuse large B-cell lymphoma), follicular lymphoma-transformed diffuse large B-cell lymphoma (DLBCL), or primary mediastinal B-cell lymphoma (PMBCL), who are subject to second-line or higher systemic therapy and who are not candidates for receive or cannot receive CAR-T cell therapy or have received prior CAR-T cell therapy. In February of this year, the National Medicines Control Administration (NMPA) approved the drug's marketing application for mainland China. The drug is intended for adult patients who have received at least two lines of systemic therapy for diffuse large B-cell lymphoma (RDLBCL) or primary mediastinal large B-cell lymphoma (PMBCL) with relapsed or refractory lymphoma.



Reference #2 Glofitamab for relapsed or refractory diffuse large B-cell lymphoma

The development of DLBCL Treatment

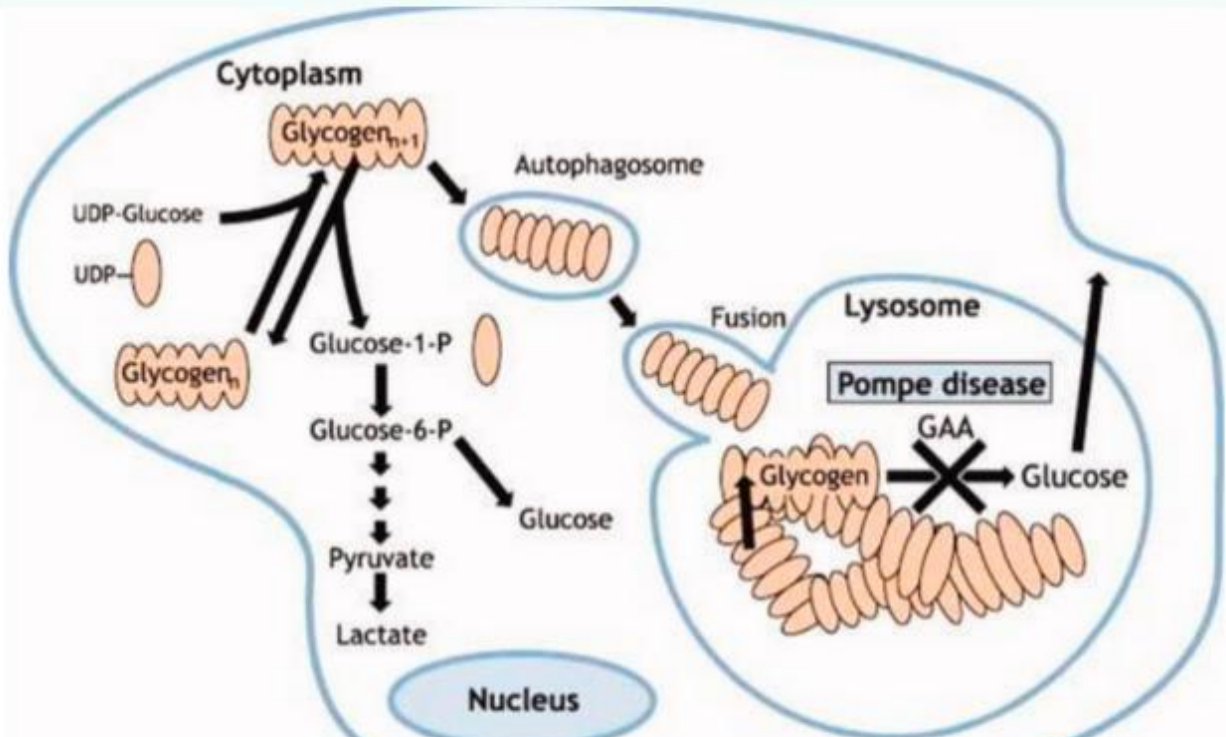
Glofitamab is a bispecific antibody capable of targeting both CD3 and CD20 in a 2:1 fashion. It contains a protein domain that targets CD3 protein on the surface of T cells (1 Fab arm for binding CD3 on T cells) and two protein domains that bind to CD20 protein on the surface of B cells (2 Fab arms for binding CD20 on B cells). As a result of this dual-targeting strategy, T cells are able to target and kill tumor cells with greater specificity. Medical researchers are testing many treatments that may do more to help people with DLBCL. If you have this condition and want information about newer treatments, ask your healthcare provider about participating in a clinical trial.

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Diagnosis and Therapy of Pompe Disease

Keywords: Pompe disease, ERT therapy, GAA enzyme, DNA genetic testing

Pompe disease, also known as type II glycogen storage disease, was first discovered by the Dutch pathologist Johannes Cassianus Pompe. It is caused by mutations in the gene encoding acid alpha-glucosidase (GAA), which is located at 17q25.3. These mutations result in reduced GAA enzyme activity, leading to ineffective glycogen degradation in the lysosomes. Consequently, glycogen accumulates in various tissues and organs such as skeletal muscles, cardiac muscles, and smooth muscles, giving rise to a range of clinical manifestations.



GAA = acid alpha-glucosidase; UDP = uridine diphosphate.

Clinical Manifestation

Pompe disease can be clinically classified into two types: the infantile-onset (onset before 1 year of age) and the late-onset (onset after 1 year of age). The infantile-onset patients are primarily present with generalized muscle weakness and hypotonia, accompanied by cardiomyopathy. On the other hand, the symptoms of late-onset patients mainly affect the trunk muscles, respiratory muscles, and proximal muscles of the limbs. For Infantile-onset patients may exhibit symptoms such as weak neck muscles, generalized muscle weakness, hearing impairment, macroglossia (enlarged tongue), feeding difficulties, sleep-disordered breathing, respiratory failure, congestive heart failure, and cardiac arrhythmias. In contrast, late-onset patients have milder symptoms compared to infantile-onset ones. They may show abnormal gait, difficult walking, respiratory problems, respiratory failure, and limb-girdle-type muscle weakness, with fewer cardiac involvements in affected patients.

Diagnosis

The progression of Pompe disease is gradual, making early diagnosis and treatment crucial for Pompe disease patients. Currently, the golden standard for diagnosis is genetic analysis. Firstly, patients should test the enzyme activity of acid alpha-glucosidase (GAA) in venous blood or dried blood spots. With signs of decreased GAA enzyme activity identified, genetic testing is required by extracting DNA from venous blood, dried blood spots, or tissue specimens. A definitive diagnosis can be made if two mutant alleles are found. If only one mutant allele is present or no mutant alleles are detected, additional tests such as skin fibroblast GAA enzyme activity testing, muscle biopsy histopathology examination, and whole-exome genetic analysis are expected. It is important to note that certain pseudo-deficient alleles, such as c.1726G>A (p.G576S) and c.2065G>A (p.E689K), may reduce GAA enzyme activity but do not lead to the development of type II glycogen storage disease. Supplementary examinations such as creatine kinase, needle electromyography, chest X-ray, electrocardiogram, echocardiography, magnetic resonance imaging, pulmonary function tests, and respiratory sleep studies can help determine the extent of organ involvement.

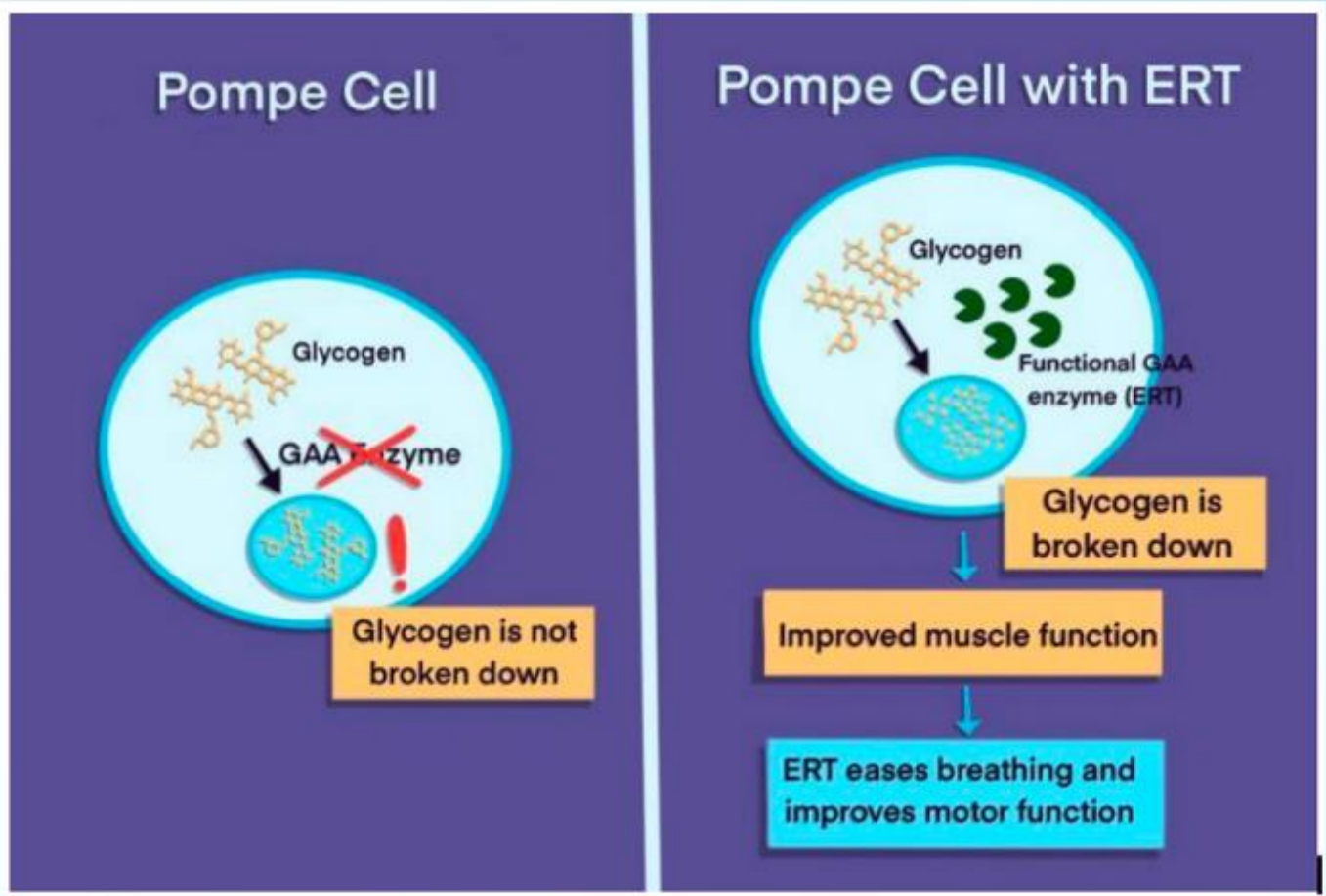
Pompe Disease Symptoms



Treatment

The current treatment methods for Pompe disease are mainly enzyme replacement therapy (ERT), followed by molecular chaperone therapy (CMT), oligonucleotide therapy, and symptomatic supportive therapy. The 2021 version of the "Chinese Expert Consensus on the Diagnosis and Treatment of Glycogen Storage Disease Type II in Children" clearly states that ERT therapy -

recombinant human acid alpha-glucosidase (rhGAA) treatment is currently the most effective treatment for all types of Pompe disease. Compared with the drug Myozyme used in rhGAA treatment, the new drug Nexviazyme (aval glucosidase alfa) performs better in improving breathing, walking, endurance functions, etc. Recent studies have also found that the combination of the new drug Cipaglucosidase Alfa and Miglustat (a chaperone protein) is more effective, but there are no accurate statistics yet. Once children with IOPD are diagnosed, ERT should be started as early as possible according to current treatment methods; children with LOPD should be given ERT if they have myasthenic symptoms and/or reduced respiratory function with increased creatine kinase. For children with cross-immunoreactive material (CRIM)-negative IOPD, immune tolerance induction therapy can be given before receiving ERT to improve their survival rate.



Summary

Pompe disease is caused by reduced acidic α -glucosidase activity, resulting in ineffective degradation of glycogen within lysosomes. This leads to its accumulation in tissue organs like skeletal muscles, cardiac muscles, and smooth muscles, causing the disease. Clinical presentations are classified as infantile-onset (symptoms appearing before 1 year) and late-onset (symptoms appearing after 1 year), with a better prognosis for the latter. Diagnosis primarily relies on α -glucosidase enzyme activity testing, complemented by DNA gene testing, taking into consideration the impact of pseudo-deficiency alleles such as c.1726G>A (p.G576S) and c.2065G>A (p.E689K) on diagnosis. Early diagnosis and treatment are crucial for disease prognosis, with rhGAA therapy being the most effective treatment for various types of Pompe disease currently. The efficacy and side effects of other therapeutic drugs are still under research.

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Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a congenital condition defined by Leo Kanner in 1943, characterized by an inherent deficiency in the ability to establish normal emotional contact with others.

Keywords: Autism Spectrum Disorder, Etiology, Diagnosis, Treatment, Children

Etiology

Genetics plays a crucial role in the etiology of autism, along with early developmental environmental factors. The identification of allele genes has revealed its genetic patterns. The current consensus suggests it is not Mendelian in inheritance and leans towards a polygenic model. About 10%-30% of rare mutations are pathogenic, for instance, mutations in TSC 1 and TSC 2 lead to tuberous sclerosis complex 6, or fragile X mental retardation 1 (FMR1; also known as FMRP) causes fragile X syndrome. Furthermore, 15%-50% of common mutations also contribute to Autism Spectrum Disorder (ASD); however, shared mutation sites for ASD have not yet been identified. Impairments in neuronal synaptic function, immune function, epigenetic dysregulation, premature birth, intrauterine infections, and exposure to antidepressants during pregnancy are also potential factors associated with ASD onset.

Epidemiology & Clinical Presentation

The global prevalence of autism in the population is approximately 1%. Autism affects males more than females, and over 70% of patients experience comorbidities. Heterogeneous neurodevelopment underlies autism, characterized by early-onset difficulties in social communication and restricted patterns of repetitive behaviors and interests. Autism patients exhibit atypical cognitive features, such as impaired social cognition and perception, executive function impairments, and non-typical sensory perception and information processing challenges. The presentation of autism patients is heterogeneous, with language ability ranging from typical to absent; cognitive development can manifest as above-average intellectual capabilities or severe intellectual disabilities. Patients might also have other comorbidities like epilepsy, and psychiatric disorders, making the diverse clinical manifestations a barrier to comprehending its pathological and physiological mechanisms.

Diagnosis

As per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), released by the American Psychiatric Association (APA) in 2013, the diagnosis primarily encompasses the following four aspects: **Impairments in Social Communication:** Individuals exhibit significant difficulties in social interaction, including establishing emotional connections, sharing interests, and understanding nonverbal social cues. **Repetitive Stereotyped Behaviors:** Individuals display repetitive, restricted behaviors, interests, and activities, such as stereotyped body movements, intense focus on specific areas of interest, and either heightened sensitivity or resistance to new changes. **Early Developmental Manifestation:** The above symptoms manifest in the early developmental stage of childhood, although they may exhibit varying characteristics as the individual grows older. **Impairment of Daily Functioning:** These symptoms significantly impact an individual's daily functioning across various domains, including social, academic, occupational, and other areas. In comparison to DSM-4, DSM-5 removes severity gradations (such as Asperger's disorder, childhood disintegrative disorder), replacing them with a unified diagnostic category: Autism Spectrum Disorder. This change aims to emphasize the diversity of autism and the continuity of symptoms, foregoing the division into discrete subtypes.



Treatment

Currently, the exact cause of autism remains unclear, leading to a lack of highly effective medications for its treatment. Experts emphasize that the primary approach for treating childhood autism should be educational intervention, with medication as a secondary option.

Comprehensive intervention measures, including educational intervention, behavior correction, and medication treatment, should be tailored to the specific circumstances of each child, considering developmental challenges and emotional behavioral anomalies.

Early comprehensive and targeted behavioral interventions can enhance social communication and reduce anxiety and aggressiveness. The focus of these interventions lies in social and communication functions, where effective medications are presently lacking and the assessment of efficacy is challenging.

Moreover, many children with Autism Spectrum Disorder (ASD) also face intellectual and/or language barriers, further complicating the assessment of treatment outcomes. In October 2006, the U.S. Food and Drug Administration (FDA) approved the use of risperidone for autistic children aged 5 to 16, addressing issues such as aggression, self-injury, and temper outbursts.

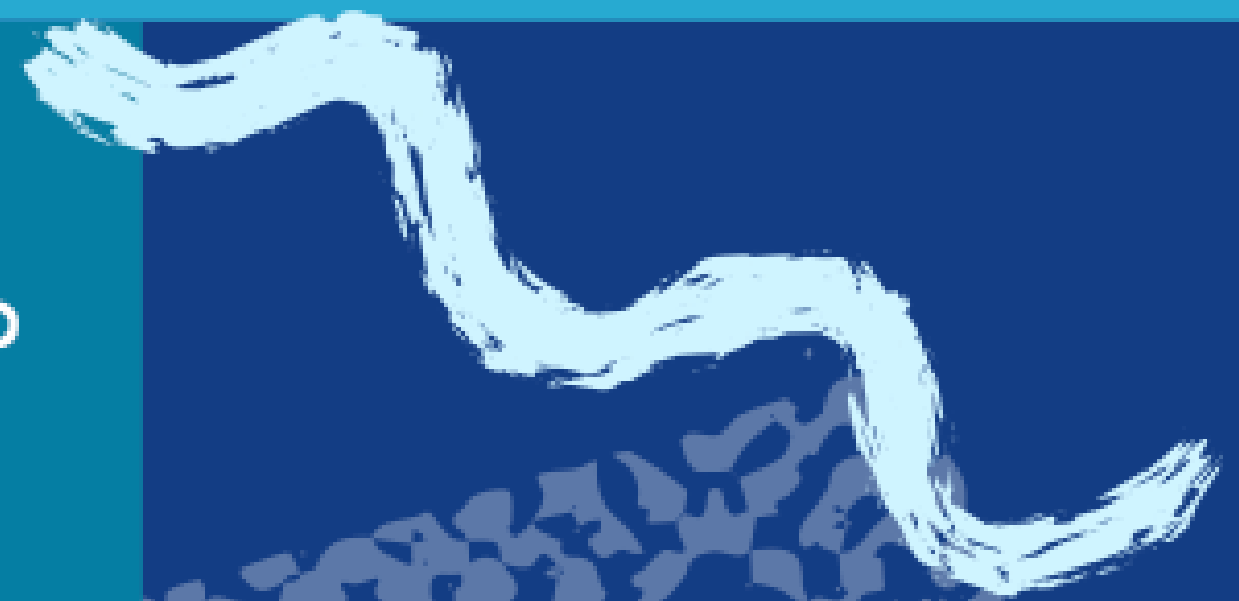
For patients with comorbid conditions, such as those with attention deficit, hyperactivity, and impulsiveness, medication options may encompass atomoxetine, methylphenidate, and clonidine, among others. While medications can alleviate comorbid symptoms, they do not directly enhance social communication. Social support also plays a vital role in the prognosis of affected children.

Summary and Outlook

Autism is an innate deficit in the ability to establish normal emotional connections with others. Its etiology remains unclear and is often accompanied by various comorbidities, which can complicate the assessment of its causes, diagnosis, and treatment outcomes. Research will continue to seek neurochemical targets for pharmacological intervention and biological predictive factors for response. Disease progression and treatment assessment will require interdisciplinary collaboration and tailored approaches for comorbidities. Early detection and intervention are crucial for effective disease management.

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ABSTRACT

"Black bile" - this is associated with the ancient Greek theory of the four humors. Ancient Greek medical pioneers, including Hippocrates, believed that depression was caused with an excess of "black bile" in the body. However, with the continuous development of human cognition, biologists have given a preliminary explanation for the etiology of depression: under the adverse intervention of social environment, interpersonal relationships and other factors; the body's hormone levels, neurotransmitter levels, intracellular signaling and other activities are affected, or even over-regulated, thus triggering a series of clinical manifestations of depression. In the biological field, scientists are continuing to conduct research on the molecular mechanisms of depression, drug therapy, diversity, gender differences, and other directions.



CONCLUSION

Nowadays, it is generally accepted that the pathogenesis of depression is related to the regulatory mechanisms of HPA and the adaptive mechanisms of the neurotransmitter system, and hypotheses about these mechanisms are constantly being demonstrated through experiments. At the present stage, drugs for depression have extreme side effects and limited application. To develop more effective antidepressant drugs, future research should take side effects into consideration and be based on respect for gender differences, experimental validation should be carried out on both genders of subjects separately. When external stimuli come, the HPA does not stop releasing cortisol even if it takes a huge risk of overloading, it does not know how serious the consequences will be, so depression is just a case of the body "doing something bad with good intentions". So, when feeling depressed and isolated, think about the fact that our body is always trying to protect us, do something that can make us happy, or get treatment and tell our body and ourselves: Don't worry, everything will be fine!

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Machanism

Regarding the causative mechanisms of depression, abnormal regulation of excitatory synapses has received much attention in recent years. Let's start with the stress response. Stress responses are activities that release hormones and other cellular mediators. These mediators promote organismal adaptation when the response is turned on and off appropriately, but they can also lead to systemic damage when the response is over-regulated or disordered. Over-activation of the hypothalamic-pituitary-adrenal axis (HPA axis), caused by prolonged exposure to a constant state of high stress, is a key mechanism of depression[1]. Stress is perceived by the brain cortex, and transmitted to the hypothalamus leading to HPA activation. HPA activity is regulated by adrenocorticotrophic hormone-releasing factor (corticotropin-releasing factor, CRF) secreted from the hypothalamus and vasopressin (AVP) released from the posterior pituitary gland. This in turn stimulates the pituitary to secrete the adrenocorticotrophic hormone (ACTH) that finally activates the secretion of glucocorticoids (cortisol in humans, which regulates activities such as neuronal survival, neurogenesis, and emotional appraisal of events, and is a key link between stress and brain functioning) from the adrenal cortex. Glucocorticoids then bind to their receptors localized within the HPA axis as well, where they exert feedback control on CRF, AVP, and ACTH secretion. As a result, the HPA axis in depressed patients is "overloaded" due to constant activation, with elevated levels of salivary, plasma, and urinary cortisol.

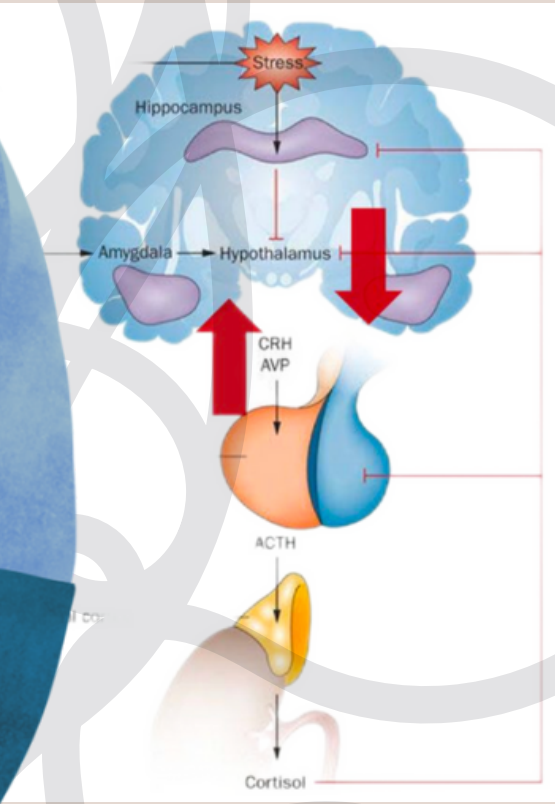


Fig. 1: Mechanism of action of HPA in response to pressure stimuli.

Nowadays, the most mainstream mechanism of depression is the HPA axis-5-HT hypothesis, and the rest of the hypotheses are related to inflammatory response, immune response, mitochondrial function, etc. The various hypotheses complement each other and explain the complex mechanism of depression together.

Fig. 2: Mechanisms of 5-HT and norepinephrine neurotransmission and sites of pharmacotherapeutic action.

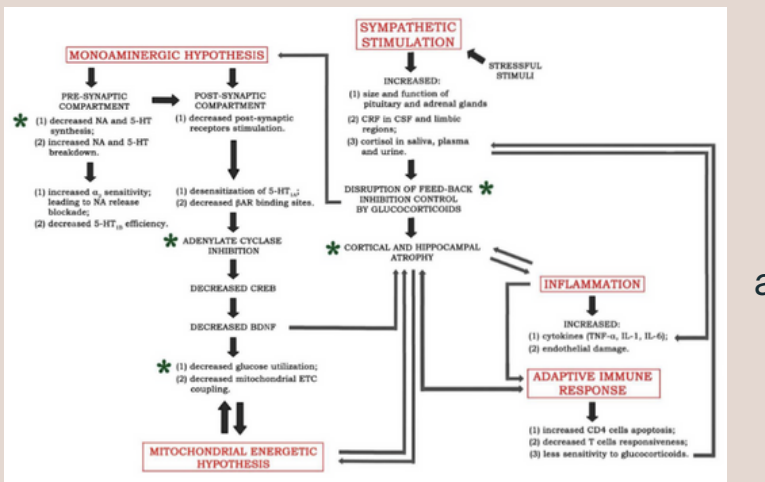
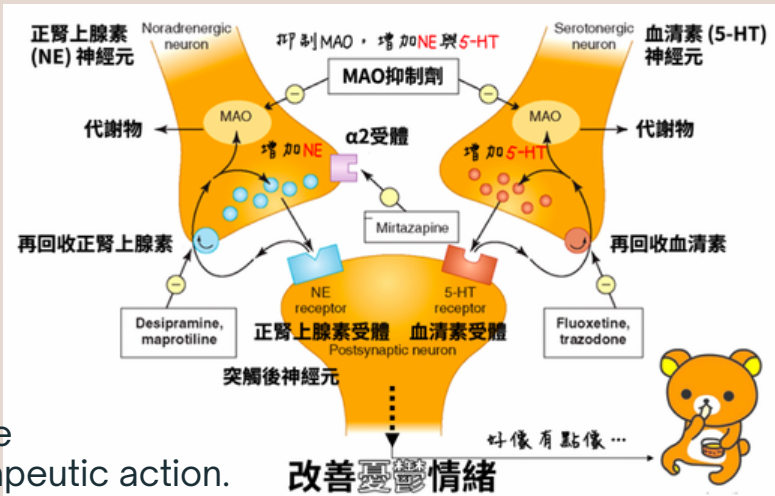


Fig. 3: Interaction between hypotheses on the pathophysiology of depression [2]

Widely used antidepressants are mainly based on the inhibition of reuptake processes, such as 5-hydroxytryptamine reuptake inhibitors (selective serotonin reuptake inhibitors, SSRIs) norepinephrine reuptake inhibitors (SNRIs), and heterocyclic antidepressants (TCAs), or based on inhibition of hormone oxidation processes, such as monoamine oxidase inhibitors (MAOIs). However, all of these drugs are associated with extreme side effects and there is an urgent need to develop highly effective psychotropic drugs with low side effects.

GENDER DIFFERENCE

Even though the causative mechanisms of depression are broadly the same, there are gender differences in the regulation of some important hormones. For example, in the presence of CRF overproduction, male LC neurons decrease their response to CRF, thereby preventing high levels of hyperarousal (disruptive feeling of being on edge). Female LC neurons are more sensitive to acute doses of CRF, and the tonic firing rate of their LC neurons is three times higher than that of males under the same conditions, so women are more likely to exhibit differences in stress responses compared to men, potentially leading to variations in symptomatology. The circuits and mechanisms responsible for these differences have not been adequately investigated because clinical studies in the past used male rodents as subjects and loosely assumed that females should show the same findings too. Today, this neglect of gender differences is beginning to be addressed. Gender differences underlie the characterization of a wide range of psychiatric disorders, and these findings allow us to conceptualize various types of gender differences in the brain, which in turn has broader implications for considering gender as a biological variable. Importantly, comparisons between genders can help to develop new treatments [4].

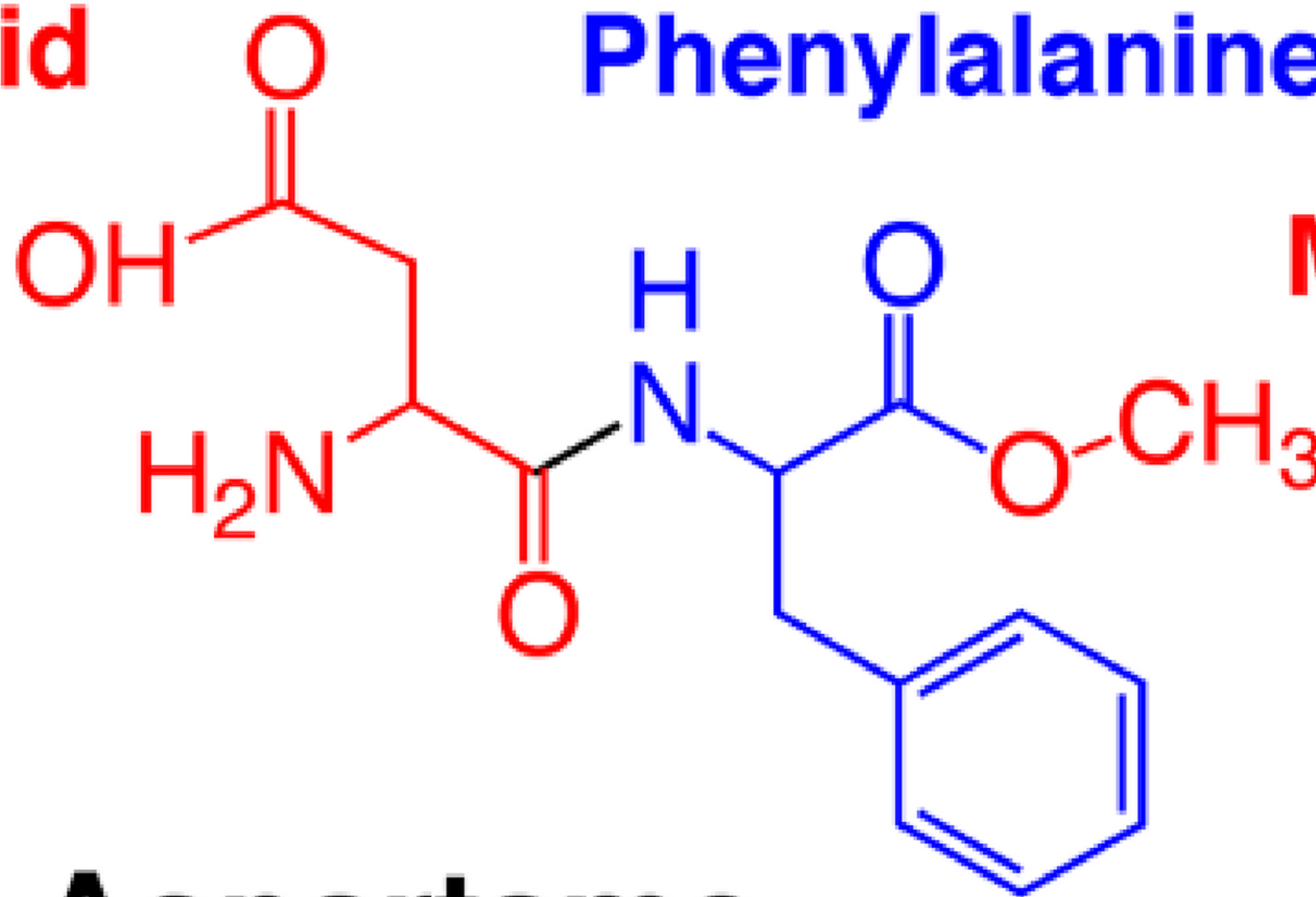
SMART MAGAZINE

Are Artificial Sweeteners
Harmful to the Human Body?

Aspartic
acid

Phenylalanine

Methanol



Aspartame

KEYWORDS:

Artificial
Sweetener

Sucrose

Diabetes

Insulin

WHAT ARE ARTIFICIAL SWEETENERS?

Artificial sweeteners are chemically synthesized compounds used to replace natural sugars or enhance the sweetness of foods. Because they are not metabolized by the human body and do not provide calories, artificial sweeteners contain fewer or no calories compared to sugar. Therefore, artificial sweeteners are widely used in low-sugar or sugar-free products in the food and beverage industry, such as diet soda and sugar-free pastries, which are frequently used in our lives. So what are some of the most common artificial sweeteners?

COMMON ARTIFICIAL SWEETENERS

Aspartame is a nonnutritive sweetener that is similar in taste to table sugar and is ~200 times sweeter. It is a low-calorie sweetener and is commonly used in beverages, energy-reduced diets, and as a tabletop sweetener.

Xylitol is a natural sugar alcohol that tastes similar to table sugar but is lower in calories. It can be used in products such as candy, gum, and toothpaste, and it also helps in preventing tooth decay.

Sodium saccharin and Saccharin are very sweet artificial sweeteners -- 300 to 500 times sweeter than table sugar. They are commonly used in drinks, pastries, and other products.

Acesulfame is an artificial sweetener used in food and personal care products. Used in food products such as dairy products, desserts, and bakery products, or in oral hygiene products such as toothpaste and mouthwash.

Sucralose, commonly known as sucralose, is a high-intensity sweetener. It is a functional sweetener based on sucrose, and its sweetness can reach 320-1000 times that of sucrose.

These artificial sweeteners are helpful for controlling sugar intake and lower-calorie diets. Moreover, there are many scientific studies that show that artificial sweeteners do not cause harm when consumed in moderation. However, in recent years, more and more studies have confirmed the effects of artificial sweeteners, indicating that long-term excessive consumption of artificial sweeteners may also pose some potential health risks. So what kind of harm do artificial sweeteners cause to the human body?

THE POTENTIAL RISKS OF ARTIFICIAL SWEETENERS

Artificial sweeteners are often highly sweet without providing excessive sugar and calories, which makes them a choice for diabetics and people who are losing weight. However, some studies suggest that long-term high consumption of artificial sweeteners may be linked to health problems such as metabolic syndrome, cardiovascular disease, and type 2 diabetes. This may be because artificial sweeteners stimulate the production of insulin, which interferes with the mechanisms that regulate blood sugar.

A team of researchers at the University of Paris Nord Sorbonne published their experimental study on artificial sweeteners in the British Medical Journal in September 2022, demonstrating a relationship between artificial sweeteners and cardiovascular disease, cerebrovascular disease, and coronary heart disease. Among them, aspartame can increase the incidence of cerebrovascular disease, while acesulfame and sucralose can increase the incidence of coronary heart disease.

Secondly, the consumption of artificial sweeteners may have an impact on an individual's taste. If highly sweet foods or drinks are consumed on a regular basis, people's palates may change to favor sweeter foods, resulting in sugar and energy. Not only that, artificial sweeteners can make people hungrier. Researchers at the University of Sydney used two groups of fruit flies that were fed artificial and natural sweeteners and showed that one group with artificial sweeteners consumed 30 percent more energy than the other. Whether the effects of artificial sweeteners, which can temporarily stimulate appetite, are beneficial is still up for debate.

To sum up, the harm of artificial sweeteners is a controversial issue. Although the frequent appearance of artificial sweeteners in our lives may make us relax our guard. Limiting the consumption of artificial sweeteners is important and needs to be widely advocated.

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AUTHOR: ICEY

TRANSLATOR: LUNETTE

HOW CAN WE PROTECT GENETIC DIVERSITY AND CONSERVE & UTILIZE PLANT GENETIC RESOURCES?

Keywords: Genetic diversity, Plant Genetic Resources Conservation, Genetic variation, crop improvement

The essay titled "Genetic Diversity and Conservation and Utilization of Plant Genetic Resources [1]" presents a comprehensive exploration of the pivotal themes surrounding genetic diversity within the context of plant species. With an academic approach, the essay delves into the intricate interplay between genetic variation, conservation efforts, and the practical utilization of plant genetic resources.

In the middle of the last century, the introduction of breeding programs laid the foundation for the "Green Revolution" and brought about an exponential increase in agricultural production. However, this led to the replacement of land races and the expansion of the monoculture cropping system. Consequently, Over 75% of the genetic diversity in PGRs and 90% of the crop varieties were lost and disappeared from farmers' fields [5]. To sustain the agricultural production system under climate change, global environmental problems, and booming population growth, "it is of paramount importance that the remaining PGRs be conserved" [1].

Drawing upon a thorough examination of existing literature and empirical studies, the essay underscores the critical importance of genetic diversity in Plant genetic resources (PGRs). Genetic diversity occurs due to genetic variation in the nucleotide sequence of DNA, chromosome mutations, and recombination during sexual reproduction. This essay elucidates how genetic variation contributes to the resilience, adaptability, and evolutionary potential of plant species, thereby influencing their ability to thrive in diverse environmental conditions and confront emerging challenges. Several factors change the genetic diversity of PGRs, including mutation, selection, genetic drift, and gene flow [2]. According to Charles Darwin's theory of evolution (1859), the advantageous genotypes will be selected and passed to the following generations. With the development of modern cultivars, significant genetic transformations can be achieved through both natural and artificial selection. For instance, plant breeders prefer to choose crop varieties with high yields, resistance to biotic and abiotic stresses, wide adaptation, non-shattering nature, large-sized seeds, early maturing, good quality traits, etc [3, 4].

One of the most essential PGRs - food and agriculture - were preserved ex-situ in gene banks that focused on inter- and intra-specific crop diversity. Till 2020, there were 711 gene banks and 16 regional/international institutions/centers spreading over 90 countries, conserving more than 5.4 million accessions from over 7051 genera [6]. Additionally, The authors delve into the legal and ethical dimensions of plant genetic resource management, highlighting international agreements and policies aimed at facilitating access to genetic resources while ensuring equitable benefits sharing. After conservation, the PGRs can be utilized for crop improvements. Diverse parents from PGRs in crossing programs can be selected to develop new crop varieties in at least 8-11 years [7]. Moreover, these varieties can be improved further by incorporating novel alleles from wild relatives or wild species. The process involves both traditional breeding methods and modern plant genetic engineering.

By synthesizing diverse aspects of genetic diversity, conservation, and utilization, the essay contributes to a holistic understanding of the intricate relationship between genetic resources and human welfare. Last but not least, we anticipate that striking a delicate balance between conserving and utilizing PGRs can benefit not only the current and future generations but also the environment.

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NEW MECHANISMS OF PROTEIN DEGRADATION IN CELLS

BY: Rachel

ABSTRACT

Eukaryotic cells contain a macromolecular protease known as the proteasome, which is capable of breaking down proteins that are modified by ubiquitin, but the proteasome can also degrade proteins that lack ubiquitin modification, but the exact mechanism of this process is still unclear. Recently researchers discovered a protein known as Midnolin, which is located in the nucleus and promotes the degradation of many transcriptional regulators through the proteasome, but these transcriptional regulators are not tagged with ubiquitin. Experiments have shown that Midnolin binds tightly to the proteasome and utilizes a mechanism that includes a free beta chain domain to "trap" substrates for catabolism. Thus, the Midnolin-proteasome pathway bypasses the traditional ubiquitination system and achieves selective degradation of many nuclear proteins.

INTRODUCTION

In mammals, transcriptional responses triggered by growth factors, neurons, and immune stimuli are mediated by a set of genes known as early genes (IEGs), which encode a family of transcription factors that include Fos, EGR, and NR4A. IEG proteins are activated in virtually all mammalian cells and promote the transcription of late response genes (LRGs), which are essential for the type-specific initial stimulus-response of cells. specific initial stimulus-response is critical. Thus, aberrant IEG expression is associated with cancer, immunodeficiency, and neurological disorders. IEG mRNA accumulates within a short time after initial stimulation, and once translated, its proteins are rapidly degraded to achieve a transient burst of protein expression. Although the mechanism of IEG transcriptional regulation is well understood, the mechanism by which IEG proteins are rapidly and specifically degraded has remained unsolved for many years.

PRINCIPLE

Eukaryotic cells rely on the proteasome, a macromolecular protease, to efficiently degrade ubiquitin-tagged proteins. It has been proposed that Fos family proteins may undergo both ubiquitination-dependent and ubiquitin-independent mechanisms upon entry into the proteasome, but the coordination of these molecular processes remains elusive. The study hypothesized the existence of a cellular pathway capable of rapidly degrading c-Fos and other IEG proteins. By utilizing a forward genetic screen, the study aims to reveal the mechanisms that control the degradation of these proteins.

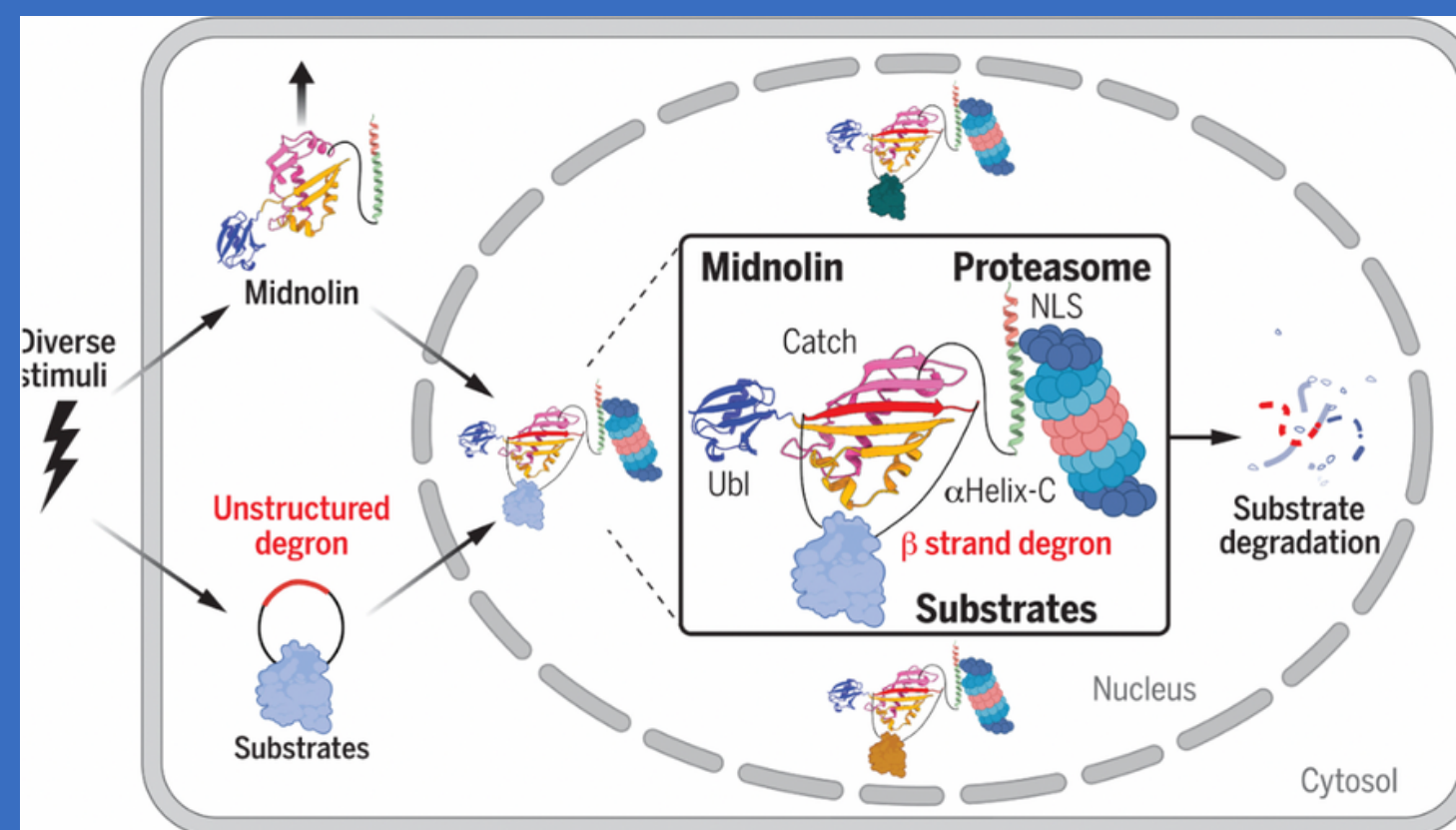
CONCLUSION

The study suggests that the Midnolin-proteasome pathway may be a general mechanism for bypassing the classical ubiquitination system in the selective degradation of nuclear proteins, especially those that are essential for transcription. Midnolin recognizes amphipathic regions within the substrate that have the simplicity to potentially form a β -strand, and thus its degradation determinants may be common structural components. Future studies need to explore how the Midnolin-proteasome pathway is regulated by multiple signals in different cell types to control transcriptional programs.

RESULTS

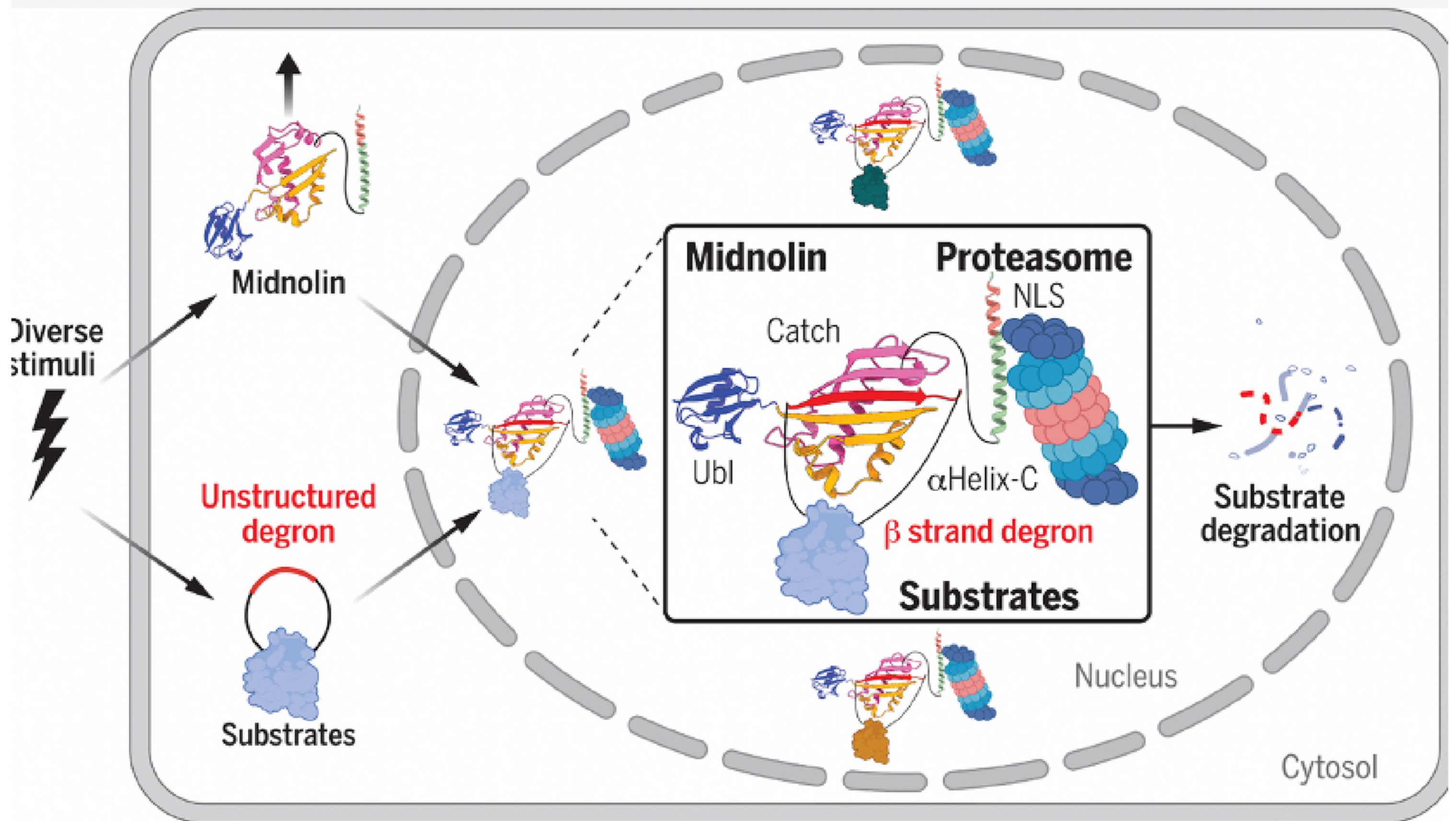
The study used a genome-wide CRISPR-Cas9 screen to explore genes that regulate the stability of IEG proteins. The results identified a protein called Midnolin in mammals that promotes proteasomal degradation in IEG proteins (e.g., c-Fos, FosB, EGR1, and NR4A1), which is not dependent on ubiquitination. In addition, Midnolin causes the degradation of a variety of other proteins, including specific transcriptional regulators in the nucleus. multiple stimuli of IEG also activate Midnolin expression, and overexpression of Midnolin induces the target to undergo ubiquitin-independent degradation.

In addition, Midnolin uses its "Catch" structural domain to engage the substrate, which is necessary and sufficient for interaction with unstructured regions within the substrate that has the potential to form a β -chain upon binding Midnolin. In addition, Midnolin binds stably to the proteasome via the C-terminal α -helix and promotes the degradation of Catch-bound targets via its N-terminal ubiquitin-like structural domain. Thus, Midnolin contains three conserved structural domains that, by acting synergistically, are able to target a large number of nuclear proteins directly to the proteasome for ubiquitination-independent degradation.



SMART MAGAZINE

New Mechanisms of Protein Degradation in Cells



ABSTRACT

Eukaryotic cells contain a macromolecular protease known as the proteasome, which is capable of breaking down proteins that are modified by ubiquitin, but the proteasome can also degrade proteins that lack ubiquitin modification, but the exact mechanism of this process is still unclear. Recently researchers discovered a protein known as Midnolin, which is located in the nucleus and promotes the degradation of many transcriptional regulators through the proteasome, but these transcriptional regulators are not tagged with ubiquitin. Experiments have shown that Midnolin binds tightly to the proteasome and utilizes a mechanism that includes a free beta chain domain to "trap" substrates for catabolism. Thus, the Midnolin-proteasome pathway bypasses the traditional ubiquitination system and achieves selective degradation of many nuclear proteins.

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AUTHOR: RACHEL



CAN THE BONE MARROW CELLS IN THE SKULL BE USED TO "TRACK" NEUROLOGICAL DISEASES?

BY: Wei Zhang

For centuries, neurological disorders have been treated as incurable diseases. Even in the present day, with technology more advanced than ever, scientists' understanding of neurological disorders remains limited to the symptoms and potential causes of the disorders, and they have no idea about the specific mechanisms of the disorders. Therefore, the ability to quickly diagnose and treat mental illnesses is a top priority for neurologists. However, today's clinical diagnosis is the opposite of the science-fiction scenario in which a single scan can provide all the information about a person's health. For example, in order to be able to determine whether a patient has Alzheimer's disease, neurologists often need to extract the right amount of cerebrospinal fluid from an elderly person's spinal cord, and then make the final decision by looking at the expression levels of various Alzheimer's-related proteins in the cerebrospinal fluid, which is undoubtedly an extremely painful process. Therefore, discovering and adopting a diagnostic method that minimizes patient discomfort has become a hot topic for cutting-edge researchers. Recently, researchers around the world have discovered the potential of cranial cells to help doctors to identify brain inflammation and draw preliminary conclusions about a patient's condition.

Researchers have used PET to track the location and extent of neuroinflammation in the skulls of people with Alzheimer's, stroke, or multiple sclerosis. They found that the skull inflammation presented differently in each disease. For example, patients with multiple sclerosis had a large inflammatory signal at the base of the skull, whereas patients with stroke or Alzheimer's disease did not. A colleague of Ertürk's, Ilgin Kolaba, corroborated this idea: "The inflammatory signal varies depending on the nature of the neurological disease. In specific areas of the skull in Alzheimer's patients, the signal is even increased, which could be a sign of disease progression. "

Since these inflammatory signals may reflect what is happening in the brain, they could serve as a potential reference for neurological diseases. These findings will help diagnose and treat stroke, Alzheimer's, and other neurological disorders with a less invasive method than the spinal tap method described above or other alternatives. If skull bone marrow cells do come into clinical use in the near future, the cost of diagnosing a range of neurological disorders will be dramatically reduced, lowering the crushing medical burden for the elderly and their relatives.

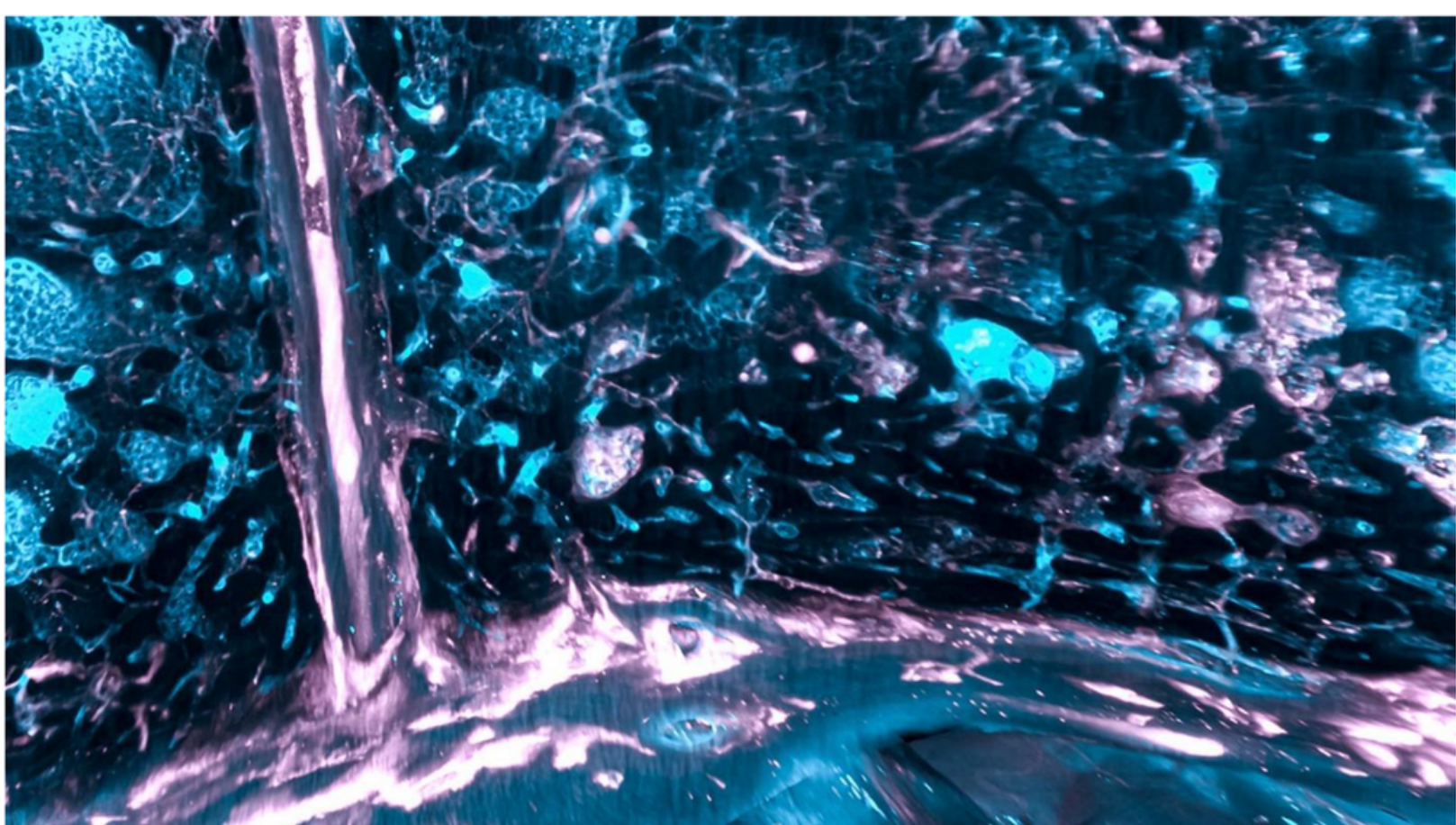


Fig 2. Three-dimensional imaging shows that it's not just the veins (pink structures on the left) that travel from the skull to the brain (below), but also the small "tunnels" (small blue vertical lines on the lower right) that connect the outer layers of the brain to the skull.

keywords: neurological diseases, bone marrow cells, Alzheimer's disease

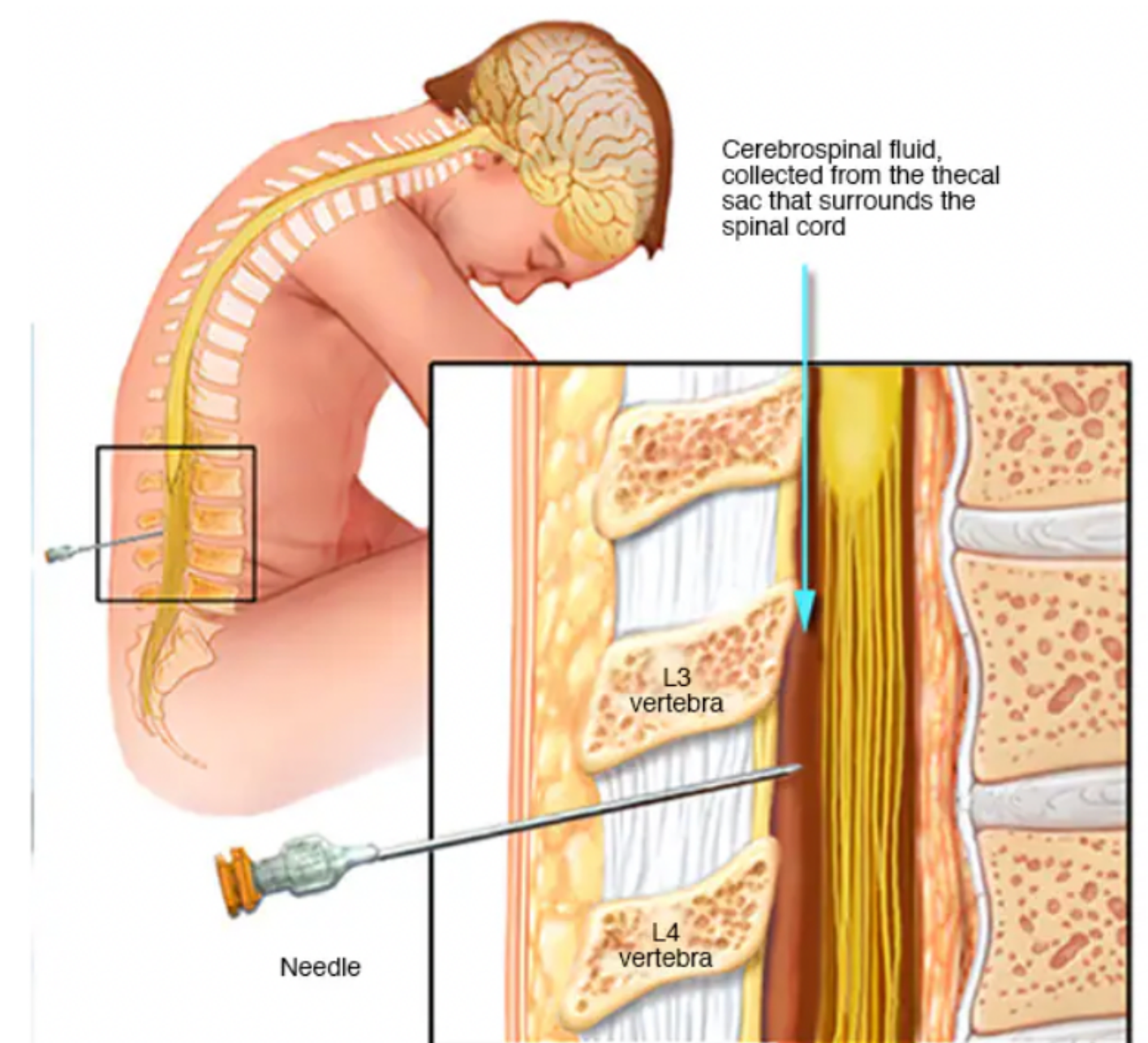


Fig 1. Existing diagnoses of Alzheimer's disease often rely on the extraction of cerebrospinal fluid (CSF), which determines the amount of amyloid and tau proteins present in the brain to diagnose Alzheimer's disease.

Ali Ertürk, a neuroscientist from Germany, and colleagues studied the behavioral differences between bone marrow cells in the skull and other bone marrow cells and found that cranial bone marrow cells rapidly differentiate and move toward the brain after brain injury, potentially suggesting that observations of bone marrow cell behavior could indirectly predict damages that occur inside the brain. bone marrow cells, along with cells in the humerus, femur, and four other bones of mice, are studied in terms of gene expression levels and proteins expressed. They found that the cells in the skull, particularly neutrophils (i.e., white blood cells), were different from those in the other bones but similar to those in the meninges, the protective membrane between the skull and the brain. And brain damage amplifies these differences. In mice with stroke symptoms, expression levels of genes related to cell migration and inflammation were much higher in the bone marrow cells of the skull than in other bone cells, suggesting that the cells respond to any lesions that occur in the brain.

This finding is undoubtedly significant, but another mystery is how skull bone marrow cells are able to travel freely between the skull and the brain. A few years ago, researchers observed in mice and humans that there are connecting "tunnels" between the skull and the meninges that allow bone marrow cells and immune cells to travel freely between the skull and the brain. Thus, the movement of bone marrow cells has largely been shown to be significantly related to brain damage. The next area of interest is the response of bone marrow cells to different neurological diseases.



2

CHINESE VERSION

English version is in the front

SMART magazine

孙悟空的定身术居然存在？脚桥核CHx10+ 神经元控制全身运动停止

概括

在这项研究中，研究人员研究了 Chx10+ 神经元在脑桥核（PPN）和中脑导水管周围灰质腹外侧柱（vIPAG）中的分布和功能。他们发现 PPN 中的 Chx10+ 神经元分布不均匀，主要集中在喙区。发现这些神经元主要参与谷氨酸信号传导。Chx10-PPN 神经元的激活诱导小鼠运动停止并暂停各种运动行为，表明它们在控制自主和可控运动中的作用。此外，研究表明 Chx10-PPN 神经元激活影响呼吸和心率，表明它们参与自主调节。然而，Chx10-PPN 和 Chx10-vIPAG 神经元激活诱导的运动停止模式是不同的，这意味着不同的神经机制。这些发现有助于我们了解运动控制及其与帕金森病等疾病的潜在相关性。

词汇

脑桥核：一组位于脑桥的核团，是脑干的一部分。脑桥在各种功能中发挥着至关重要的作用，包括大脑和脊髓不同部分之间的信号传递。

Chx10 神经元：具有吻侧偏向的谷氨酸能 PPN 神经元亚群。

神经递质表型：这些神经元产生和释放以将信号传输到其他神经元或靶细胞的特定神经递质。

光遗传学：利用光来控制经过基因修饰的光敏感特定神经元活动的技术。在这种情况下，使用光刺激来操纵 Chx10-PPN 神经元。

实验过程

桥核 Chx10 的分布

科学家们试图探索 PPN 谷氨酸能神经元中脑桥核 Chx10 的分布。首先，他们将 Chx10 Cre 小鼠与 R26R tdTomato 细胞系杂交，该细胞系用于永久标记 Chx10+ 神经元。结果显示，Chx10+ 神经元沿 PPN 的头尾轴分布不均匀，主要分布在头侧。

Chx10+ 的神经递质表型

随后，科学家们研究了 PPN 中 Chx10+ 神经元的神经递质表型。在 Chx10 Cre 切片中，他们使用 RNAscope 结合 eYFP 免疫染色对 Vglut2 mRNA 进行原位杂交。R26R EYFP 报告小鼠中的所有 Chx10+ 神经元均表达 eYFP，并量化其两个或多个基因的同时表达。大多数 Chx10+ 细胞表达为 Vglut2 mRNA（89.67% ± 0.75%）。这表明这些神经元主要使用谷氨酸作为神经递质。谷氨酸是一种兴奋性神经递质，这意味着它可以增强与之通信的神经元的活动。

在电机控制中发挥作用？

这些结果使他们能够利用光遗传学方法来研究 Chx10-PPN 神经元是否在运动控制中发挥作用。小鼠在两种不同的环境中进行了测试：第一种是用于评估 Chx10-PPN 神经元对随意运动的影响的线性通道。这种环境可能使研究人员能够观察运动的变化并评估这些神经元如何影响基本运动功能。第二个是圆柱形竞技场，用于评估该神经元对其他可控运动（例如梳洗或直立行走）的影响。

测试结果显示，在第一种线性通道中，通过单侧激活 Chx10-PPN 神经元，这诱发了运动停滞，结束刺激时几乎瞬时恢复。在第二种圆柱形旷场（cylindrical arena）中，激活 Chx10-PPN 神经元会短暂暂停小鼠行走、梳理毛发和站立的行为。以上结果表明小鼠运动停滞是由于 Chx10-PPN神经元的激活。

呼吸和心率的影响

既然 PPNs 在自主神经调节中发挥着重要作用，那么 Chx10-PPN 激活是否也具有肢体运动输出之外的影响，因此他们研究了其对呼吸和心率的影响。使用同步全身体积追踪（WBP）、无线心电图（ECG）和其他活动追踪，他们记录了自由清醒的小鼠以随机间隔向 Chx10-PPN 神经元发射信号，使用了蓝光或黄光作为控制，传递光刺激。

摘要

孙悟空有一种名叫“定身术”的能力，能把生物定在原地一动不动。而在科技高速发展的今天，这项本领将要被科学家实现出来了！近日，科学家们在小鼠大脑中发现一组神经元，当它受到刺激时，会导致小鼠停止所有运动，包括正常的呼吸节奏。当结束刺激时，小鼠会准确地从停止的地方开始运动，分毫不差。科学家称，这项研究可能有助于了解主要症状为运动迟缓的帕金森症与其发病机制。

关键词

神经元，脑桥核，谷氨酸（PPN），全身体积描记法（WBP），神经轴，帕金森病（PD），电动立体定位注射系统（Stereo Drive Robot Stereotaxic, Neurostar）

实验介绍

科学家们有一项新发现，使我们对突然停止运动时大脑中会发生什么有更近一步的了解。“我们在中脑中发现了一组神经细胞，当它受到刺激时，它们会停止所有运动。不仅仅是走路等日常行为，甚至包括了所有形式的运动活动。它们可以使小鼠停止呼吸或呼吸缓慢，心率减慢。”该研究项目的教授 Ole Kiehn 说道。“有多种方法可以停止运动。这些神经细胞的特别之处在于，一旦激活，它们会导致运动暂停或冻结。就像将电影设置为暂停一样。演员的动作突然在现场停止。”

研究人员刺激的神经细胞存在于中脑中称为“蒂脑桥核（PPN）”的区域，它们通过与 Chx10 的特定分子标记而与其他神经细胞不同。

PPN 在所有脊椎动物中都是通用的，包括人类。因此，即使这项研究是在老鼠身上进行的，科学家们认为有高机率也适用于人类。

结果

结果显示，激活Chx10-PPN神经元会使小鼠的活动暂停，同时，它们表现出呼吸暂停，而在激活结束后的活动期间，小鼠的呼吸和心率十分迅速地恢复到激活前水平。令人惊讶的是，在没有任何人工干预的情况下，小鼠也会产生类似的运动和停滞的表现。这些结果证实，在Chx10-PPN神经元激活时观察到的行为模式在平时也依然存在，证实了有自然因素在影响着小鼠。

中脑导水管周围灰质腹外侧柱(vIPAG)谷氨酸能神经元的激活引起与先天恐惧反应相关的整体运动停滞，且vIPAG中表达Chx10的谷氨酸能神经元亚群也引起冻结反应。因此这里科学家们继续探究刺激Chx10-vIPAG神经元是否会引起与Chx10-PPN刺激相似的运动停滞。

结果显示，在第一种线性通道中，Chx10-vIPAG神经元的单侧光刺激激活也能有效阻止正在进行的运动，但与 Chx10-PPN激活不同的是，Chx10-vIPAG激活诱发运动停止的潜伏期显著长于Chx10-PPN激活时的时间，且Chx10-vIPAG激活结束后小鼠的运动活性并不会恢复到激活前水平。在第二种圆形旷场（cylindrical arena）中，Chx10-vIPAG激活结束后小鼠无法继续之前的运动步骤。在对小鼠呼吸和心率频率的监测过程中，发现Chx10-vIPAG激活诱导的呼吸和心率的抑制程度明显低于Chx10-PPN激活所诱导的。以上结果表明Chx10-PPN诱发的整体运动停滞与Chx10-vIPAG诱发的整体运动停滞无关。

综上所述，本研究发现了PPN Chx10+以及Chx10-vIPAG神经元激活时诱发的脑干命令，该命令导致了整体运动停滞。整体运动停滞伴随着呼吸暂停和心率降低。鉴于PPN在帕金森发病机制中的意义，该文章可能具有潜在的价值。

“定身术”带给人们的好处

定身术或能帮助人们进一步了解帕金森病的症状以及帮助了解帕金森病发病机制。PPN技术已被用于深部脑刺激方法的靶标，以改善PD症状，针对PPN的深部脑刺激以缓解PD运动功能障碍的成功方法很可能应该避免细胞核的喙部，以防止Chx10人群的参与。

"运动停滞或运动缓慢是帕金森病的主要症状之一。我们推测，在帕金森病中，PPN 中的这些特殊神经细胞被过度激活。这将抑制运动。"

Ole Kiehn 总结说："因此，这项研究主要关注的是神经系统控制运动的基本机制，最终可能会帮助我们了解帕金森病某些运动症状的原因。"

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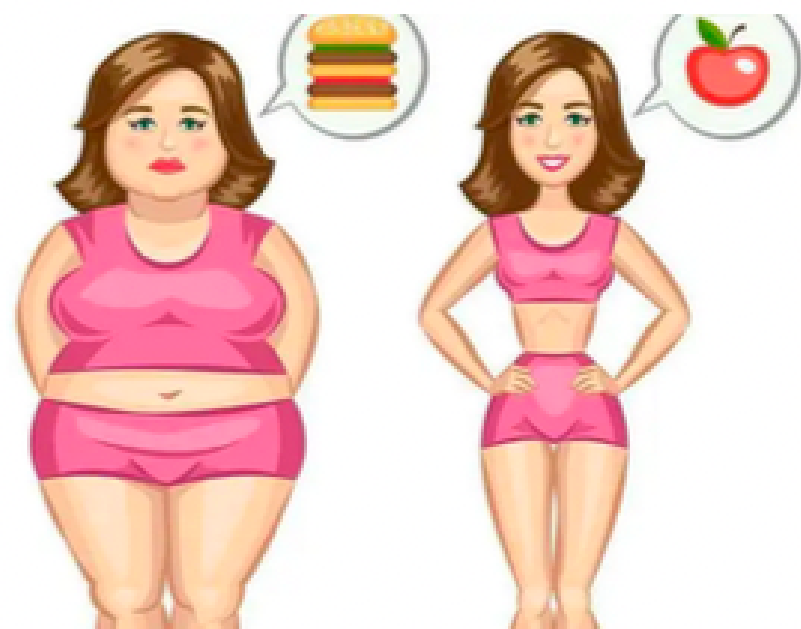
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司美格鲁肽

作者：ZHIYUAN LI

关键词：减肥，体重，减肥药，心脏病，糖尿病



许多人都十分在意自己的体型，会透过运动、节食或使用减肥药等方法来降低体重。其中，运动无疑是最健康的减肥方法，但对于时间紧张和一些懒惰的人来说，减肥药反而成为了他们的首选。

神奇的是，减肥药似乎和治疗糖尿病的降糖药有着密不可分的关系。双胍类、列净类、列汀类和阿卡波糖等常见的降糖药都会减轻体重。在 2023 年 8 月，诺和诺德公司宣布其旗下一款降糖药物——司美格鲁肽，在降低血糖的同时，还具有减肥以及减少不良心血管事件发生的概率等作用

大大减少心血管事件

司美格鲁肽是一款 GLP-1 受体激动剂，作为一种肠促胰岛素，以葡萄糖浓度依赖的方式促进胰岛素分泌，抑制胰高血糖素分泌、降低血糖，同时能延缓胃排空从而抑制食欲。因其可以降低体重，因此也被认为可以减少心血管事件的发生。在本次诺和诺德公司的随机，双盲，平行组和安慰剂组对照 III 期试验中，采用司美格鲁肽 2.4mg，在长达 5 年的时间里，作为标准治疗的辅助用药，用于预防心血管疾病、超重或肥胖、无糖尿病史患者发生重大不良心血管事件（MACE）的风险。试验包括了 17604 名年龄 45 岁及以上，患有超重或肥胖，合并心血管疾病，而无糖尿病史的成年人。主要终点为首次发生 MACE，包括心血管死亡、非致死性心肌梗死或非致死性卒中。

随着实验的结束，只有 1270 名患者发生了 MACE。同时与安慰剂对比，连续 5 年每周一次的皮下注射 2.4mg 司美格鲁肽可以减少 20% MACE 的发生。

在同行的衬托下遥遥领先

根据诺和诺德公司报告，根据 IIIb 期试验结果，司美格鲁肽注射液 2.4mg 治疗量下 68 周减重率为 15.8%（即一位 70kg 的患者在 68 周后可以减重到 58.94kg），效果显著。司美格鲁肽的优势不仅如此，还有：

- 1) 在 2021 年 424 项随机对照（RCT）实验和网络荟萃分析显示，司美格鲁肽注射液 9 大类 21 种降糖药中，表现出最优的减重效果。另有研究证实，司美格鲁肽较同公司的利拉鲁肽也有优势。
- 2) 司美格鲁肽只需要每周一针，相对于其他市面上其他种类的 GLP-1 受体激动减肥针需要每天一针，它更加便捷。
- 3) 他是获得 FDA 批准的可用于减肥的降糖药。
- 4) 和其他减肥药不同的是，司美格鲁肽不仅可以控制血糖和减肥，相对于其他药品，他还可以出色的降低心血管事件的发生，所以 FDA 也批准了它可以用于第二型糖尿病合并心血管疾病的患者。

FDA NEWS RELEASE

FDA Approves New Drug Treatment for Chronic Weight Management, First Since 2014

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For Immediate Release: June 04, 2021

Español

Today, the U.S. Food and Drug Administration approved Wegovy (semaglutide) injection (2.4 mg once weekly) for chronic weight management in adults with obesity or overweight with at least one weight-related condition (such as high blood pressure, type 2 diabetes, or high cholesterol), for use in addition to a reduced calorie diet and increased physical activity. This under-the-skin injection is the first approved drug for chronic weight

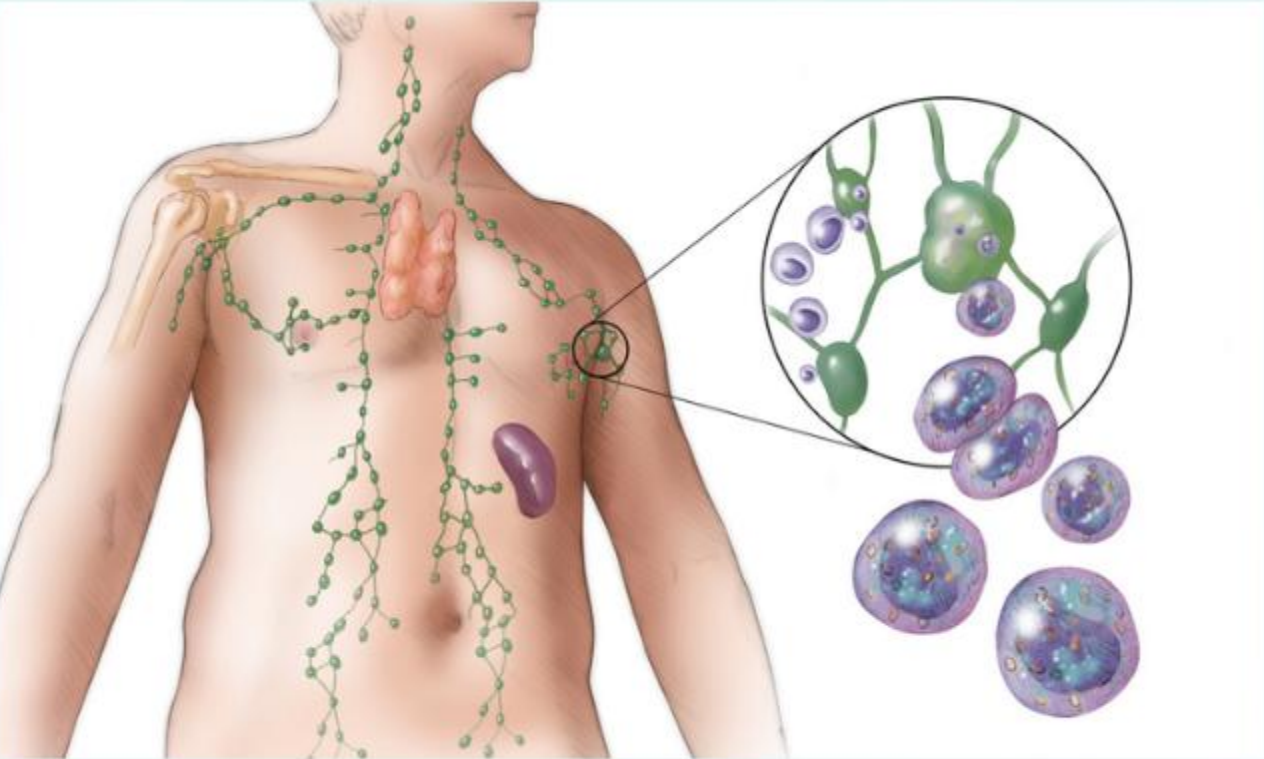
management in adults with general obesity or overweight since 2014. The drug is indicated for chronic weight management in patients with a body mass index (BMI) of 27 kg/m² or greater who have at least one weight-related ailment or in patients with a BMI of 30 kg/m² or greater.

尽管随着科技和药物的发展，我们有越来越多的方式可以减轻体重。但根据实验研究，运动仍然是减肥和控制心血管事件的最好方法。因此，在此呼吁大家，不妨每天抽空运动，才可以获得真正的健康。

淋巴瘤是什么？在淋巴结内生长的肿瘤是否属于淋巴瘤？

关键词汇：淋巴瘤、癌症、医学突破 作者：Sindy；中文翻译：Lily Gu

淋巴瘤是由于白细胞里的一种淋巴细胞不受控制的生长而引起的疾病。我们体内的淋巴细胞通过在淋巴系统中穿梭来帮助我们的免疫系统对抗感染。淋巴细胞分为两种类型：T 淋巴细胞（T 细胞）和 B 淋巴细胞（B 细胞）。在所有的淋巴瘤类型中，弥漫性大的 B 细胞淋巴瘤（DLBCL）占据了非何杰金淋巴瘤（NHL）临床病例的三分之一左右。自从发现以来，这种类型的淋巴瘤通常被称之为“有侵略性”或“中度至重度恶性”的淋巴瘤。因 DLBCL 的异质性，不同的种类患有不同的临床特征、基因变化和治疗反应。



参考文献 #1 给患有弥漫性大B细胞淋巴瘤的患者测量预后病情

淋巴瘤常见吗？ 发病率是多少？

非何杰金淋巴瘤（NHL）是最常见的肿瘤之一，占据所有癌症的 4% 左右。尤其是近几年来，淋巴瘤的发病率呈现明显的上升趋势。根据中国抗癌协会（CACA）的数据，淋巴瘤在中国年例的发病约为75400 例，发病率为每 10 万人中有 4.75 例，死亡人数大概是 40500 例，死亡率为每 10 万人中有 2.64 例。

DLBCL的治疗发展

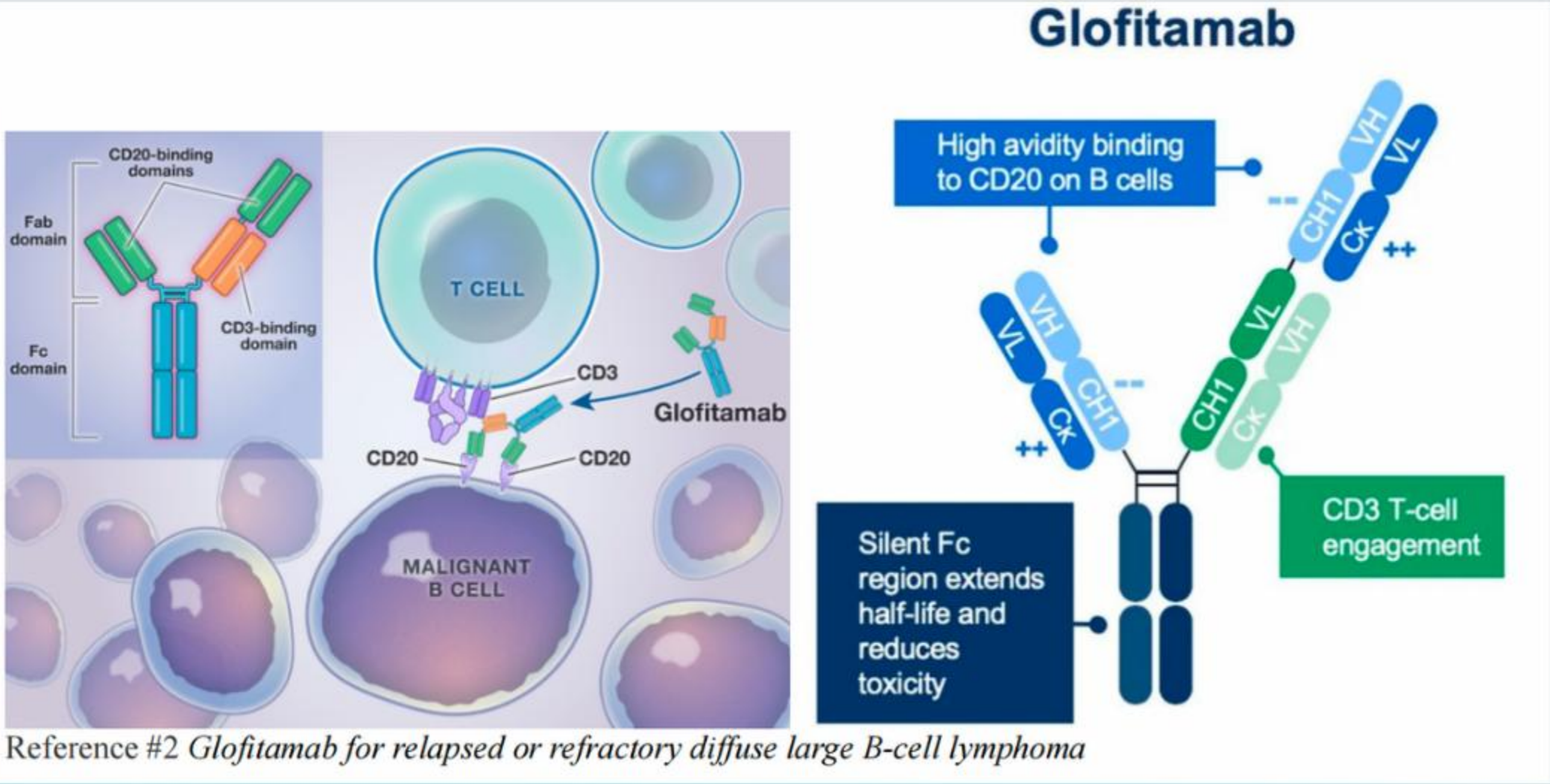
r-CHOP 治疗方案
r-CHOP（利妥昔单抗 + 环磷酰胺 + 阿霉素 + 长春新碱 + 泼尼松）是目前 DLBCL 的标准治疗方案，但是对于 30-40% 的患者来说，抵抗性和复发性仍构成一个挑战。

干细胞移植
在治疗后出现难治的或复发性病情的 DLBCL 患者通常要接受干细胞移植。在大多数情况下，干细胞移植是自体移植，这意味着患者会在手术前接收自己的干细胞。在其他情况下，患者将接受异体移植，接收来自另一个供体的干细胞。与 r-CHOP 治疗方案类似，临床试验显示，即使在完成治疗后，复发或难治性大 B 细胞淋巴瘤的发生率也很高。

Glofitamab-gxbm (Columvi, Genentech, Inc.)
2023年6月15号，食品和药物管理局加速批准了 Glofitamab-gxbm (Columvi, Genentech, Inc.) 用于治疗复发或难治性弥漫性大 B 细胞淋巴瘤，不另行指定 (DLBCL, NOS) 或接受两种或两种以上系统治疗后，由滤泡性淋巴瘤引起的大 B 细胞淋巴瘤。研究显示，接受 Columvi 治疗的患者缓解率（完全缓解和部分缓解）达到 56%，其中完全缓解率为 43%，缓解时间持续大约为 1.5 年。今年 3 月 25 日，该药物被加拿大卫生部批准使用给患有 R/R DLBCL 的成年患者（复发或难治性弥漫 B 细胞淋巴瘤），滤泡性淋巴瘤转化弥漫性大 B 细胞淋巴瘤 (DLBCL)，或原发性纵隔 B 细胞淋巴瘤 (PMBCL)，这些患者接受过二线或更高级别全身治疗的，并且不适合接受或不能接受 CAR-T 细胞治疗或先前接受过 CAR-T 细胞治疗。今年 2 月，国家药品监督管理局 (NMPA)，批准了该药物在中国大陆市场的申请。这一药物适用于接受过至少两种针对弥漫性大 B 细胞淋巴瘤系统治疗 (RDLBCL)，或原发性纵隔大 B 细胞淋巴瘤 (PMBCL)，且伴有复发或难治性淋巴瘤的成年患者。

Glofitamab 在难治性弥漫大 B 细胞淋巴瘤

GGlofiramab 是一种双特异性抗体，能够以 2：1 的方式同时靶向 CD3 和 CD20。它包含一个靶向 T 细胞表面 CD3 蛋白的蛋白结构域（1 个 Fab 臂用于结合 CD3 蛋白在 T 细胞上）和两个结合 B 细胞表面 CD20 蛋白的蛋白结构域（2 个 Fab 臂用于合并 B 细胞上的 CD20 蛋白）。由于这种双重靶向策略，T 细胞能够以更高的特异性靶向并杀死肿瘤细胞。这些医学研究的目标是寻找更有效的 DLBCL 治疗方法，如果您想了解更多最新治疗信息，可以咨询您的医疗保健提供者，关于参加临床试验的事宜。

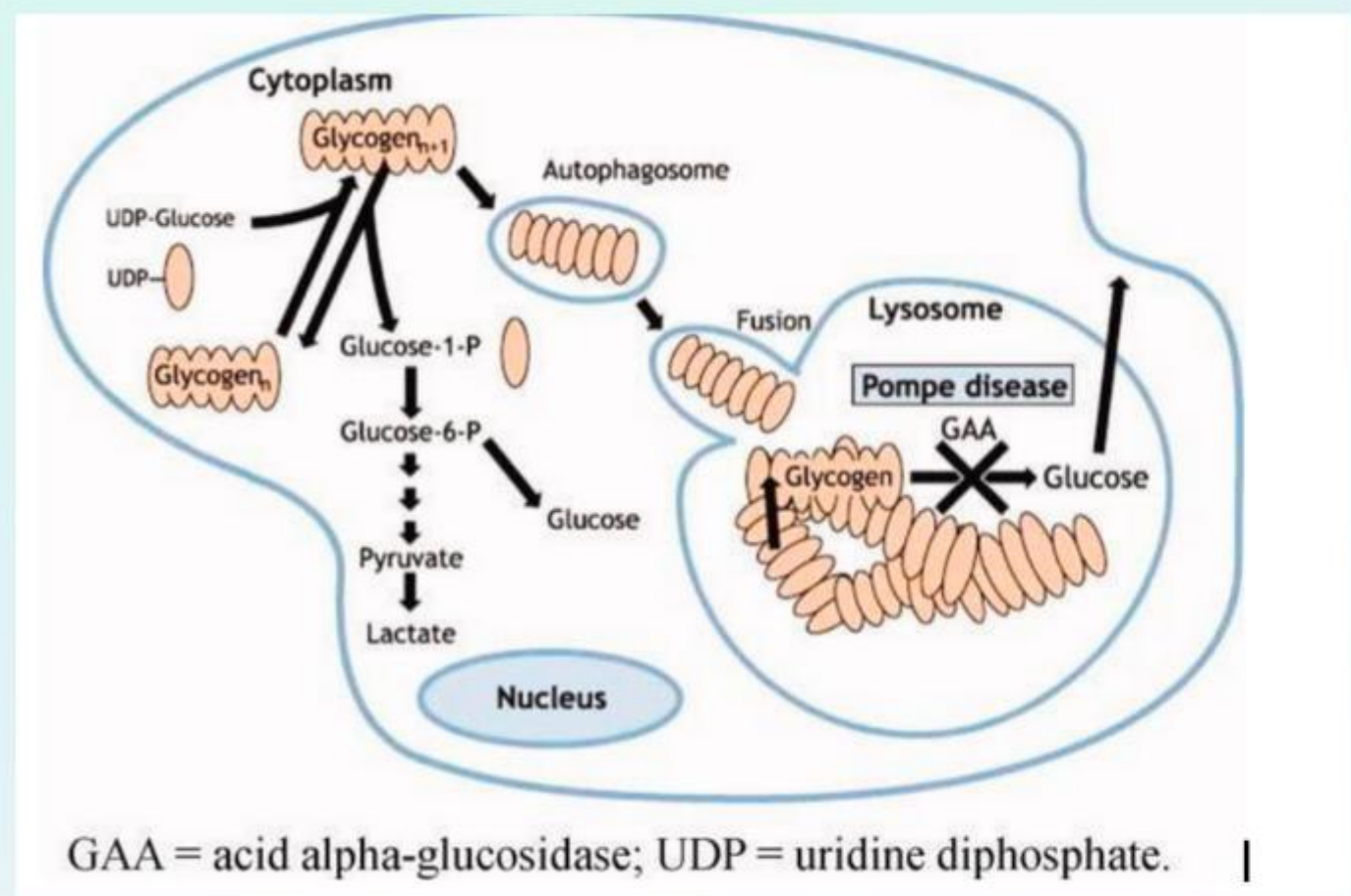


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庞贝病的诊治

关键字：庞贝病、ERT 疗法、GAA 酶、DNA 基因检测

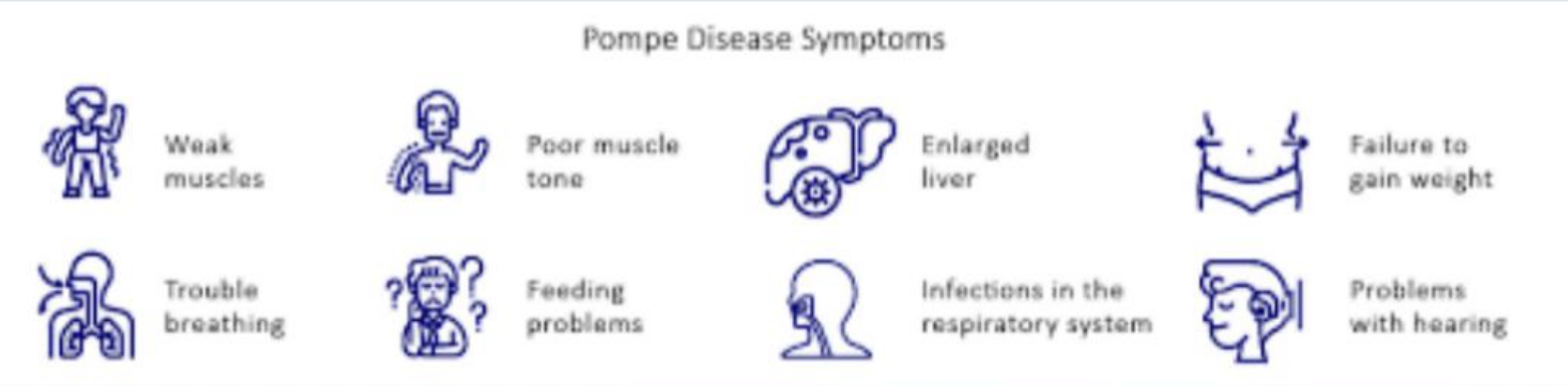
庞贝病又称糖原贮积病Ⅱ型，最初由荷兰病理学家 Johannes Cassianus Pompe 首次发现。患者由于位在 17q25.3 编码的酸性 α-葡萄糖苷酶（acid alpha-glucosidase，GAA）基因突变，导致 GAA 酶活性降低，造成糖原在溶酶体内不能被有效降解，进而沉积于骨骼肌、心肌、平滑肌等组织器官中，最终引发的一系列临床表现。



参考文献 #1 给拥有弥漫性大B细胞淋巴瘤的患者测量预后病情

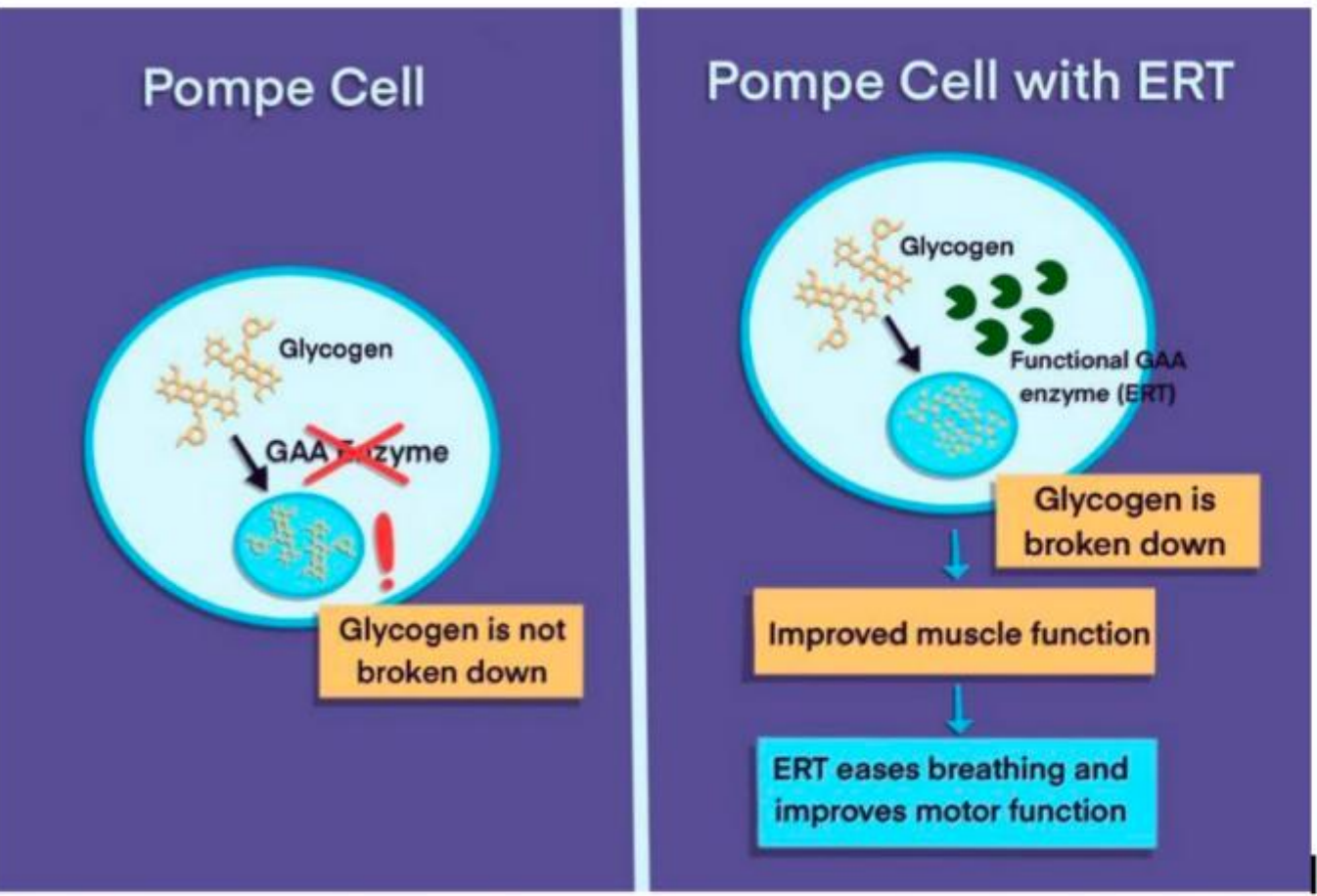
诊断

庞贝病的发展是渐进的，因此早期的诊断及治疗对于庞贝病患者至关重要。目前诊断的标准为基因分析。首先，患者应检测静脉血或干血斑中 GAA 酶的活性。若发现 GAA 酶的活性降低，再进一步通过提取静脉血、干血纸片样本或组织标本的 DNA 进行基因检测。若发现双等位基因突变则可确诊；若只有单个等位基因突变或未发现等位基因突变，则进行皮肤成纤维细胞 GAA 酶活性检测、肌肉活检病理检查和全外显子基因分析等。值得注意的是，假性缺陷等位基因如 c.1726G > A (p.G576S) 与 c.2065G > A (p.E689K) 也会降低 GAA 酶的活性，但并不导致糖原累积病Ⅱ型的发生。辅助检查如肌酸激酶、针极肌电图、胸 X 线片、心电图、超声心动图、核磁共振成像、肺功能、呼吸睡眠检测等，可帮助明确器官受累情况。



治疗

目前治疗庞贝病的方法主要为酶替代疗法（enzyme replacement therapy，ERT），再以分子伴侣疗法（chaperone therapy，CMT）、寡核苷酸药物以及对症支持疗法辅助治疗。2021 版《儿童糖原累积病Ⅱ型诊断及治疗中国专家共识》明确指



ERT 疗法——重组人酸性 α-葡萄糖苷酶（rhGAA）治疗，是目前针对各型庞贝病最有效的治疗方法。而与 rhGAA 治疗所使用的药物 Myozyme 相比，新药 Nexviazyme（avalglucosidase alfa）在改善呼吸、行走、耐力功能等方面表现更佳。近期的研究也发现，新药 Cipaglucosidase Alfa 和 Miglustat（一种伴侣蛋白）联用的治疗效果更优，但目前尚未有准确的统计数字。IOPD 患儿一旦确诊，以目前的治疗方法应尽早开始 ERT；LOPD 患儿如果有肌无力症状和（或）呼吸功能减退伴肌酸激酶增高时应给予 ERT。对于交叉免疫反应物质（CRIM）阴性的 IOPD 患儿，在接受 ERT 前可给予免疫耐受诱导治疗以提高其存活率。

总结

庞贝病由酸性 α-葡萄糖苷酶活性降低导致，糖原在溶酶体内不能被有效降解，沉积于骨骼肌、心肌、平滑肌等组织器官中而致病。其临床表现分为婴儿型（发病 < 1 岁）和迟发型（发病 > 1 岁），迟发型预后较婴儿型更好。诊断主要依赖于 α-葡糖

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自闭症谱系障碍

病因·

遗传学在自闭症的病因学中起着关键作用，与发育早期的环境因素有关。目前等位基因的鉴定已经揭示了其遗传模式。目前共识认为，它不完全符合孟德尔式遗传，更倾向于多基因模型。其中 10~30% 的罕见突变是致病的，例

如 TSC 1 和 TSC 2 突变导致结节性硬化症复合体 6 或脆性 X - 智力低下 1

(FMR 1, 又称 FMRP) 导致脆性 X 综合征；15~50% 常见的突变也会导致自闭症谱系障碍

(ASD)，然而目前尚未发现 ASD 的共同突变位点。神经元突触功能障碍、免疫功能和表观遗传失调、早产、宫内感染、妊娠期间抗抑郁药物的暴露也可能与 ASD 发病相关。

自闭症谱系障碍 (Autism Spectrum Disorder, ASD) 是由利奥坎纳在 1943 年定义为一种天生的、无法与他人建立正常情感接触的能力缺陷。

关键字：自闭症谱系障碍、病因学、诊断、治疗、儿童

流行病学和临床表现

全世界人口中自闭症患病率约为 1%，且自闭症对男性的影响大于女性个体，并且大于 70% 的患者患有并发症。自闭症由异质性神经发育引起，其特征在于社交沟通的早期发作困难以及异常受限的重复行为和兴趣。自闭症患者具有非典型认知特征，例如受损的社会认知和社会感知、执行功能障碍以及非典型感知和信息处理障碍。自闭症患者的表现具有异质性，如语言能力水平可表现为正常或缺失；认知发展方面也可表现为高于平均水平的智力水平或严重的智力残疾。患者还可能患有其他并发症，如癫痫、精神病合并症等，临床表现的广泛异质性成为了理解其病理生理机制的障碍。

诊断

根据由美国精神病协会 (APA) 于 2013 年发布的 DSM-5 (《精神疾病诊断与统计手册》第5版)，诊断主要分为以下四个层面：

1. 社交沟通困难：个体在社交互动方面表现出明显的障碍。包括与他人建立情感联系、共享兴趣、理解非言语性的社交信号等方面的困难。
2. 刻板重复行为：个体表现出刻板、重复、限制性的行为、兴趣和活动。包括刻板化的肢体动作、沉浸于特定兴趣领域、对于新事物变化的过度敏感或过度抵制等。
3. 症状在早期发育阶段显现：以上症状在早期儿童发育阶段就已经显现，尽管可能会随着年龄的增长而呈现出不同的特点。
4. 症状影响日常功能：这些症状会对个体的日常功能产生显著影响，包括社交、学校、职业和其他领域。

DSM-5 与 DSM-4 相比，取消严重度分级（如亚斯伯格综合症、儿童孤独症障碍等），取而代之的是一个统一的诊断范畴：自闭症谱系障碍。此改变旨在强调自闭症的多样性和症状的连续性，不再将其分为离散的亚型。



治疗

目前自闭症的病因尚不清楚，因此缺乏治疗的特效药。专家们强调，治疗儿童自闭症的主要方法应是教育干预，次之才是药物治疗。根据儿童的具体情况，包括发育障碍和情绪行为异常，应采取综合干预措施，包括教育干预、行为矫正以及药物治疗。早期全面和有针对性的行为干预可以改善社会沟通，减少焦虑和攻击性。干预的焦点在于社交和沟通功能，目前缺乏有效的药物，且疗效难以评估。而且许多 ASD 患儿还具有智力和/或语言障碍，这让评估治疗效果更具挑战性。美国食品药品监督管理局（FDA）在 2006 年 10 月批准了利培酮用于 5~16 岁的自闭症儿童，用于治疗攻击、自伤和发脾气等行为问题。对于患有共病的患者，如伴随注意力缺陷、多动和冲动症状的情况，药物选择可以包括托莫西汀、哌甲酯、可乐定等。药物可以减少共病症状，但不能直接改善社会沟通。社会支持对于患儿的预后也是极其重要的。

总结和展望

自闭症是一种天生的、无法与他人建立正常的情感接触的能力缺陷。其病因尚不明确，常伴有多种共患病，易对其病因、诊断以及疗效的评估造成干扰。研究将继续寻找用于药物干预的神经化学靶点和反应的生物学预测因子；病情及疗效评估需要多学科联合，可针对共患病进行治疗。早期发现和早期干预对于疾病治疗很关键。

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简介

“黑胆汁”——这跟古希腊医学中的四个元素有关。以希波克拉底为代表的古希腊医学先驱们认为抑郁症是体内“黑胆汁”过多造成的。但随着人类认知的不断发展，生物学家对抑郁症的病因给出了初步解释：在社会环境、人际交往关系等因素的不良干预下，体内激素水平、神经递质水平，细胞内的信号传递等活动受到影响，甚至过度调节，从而引发一系列抑郁临床表现。就生物领域而言，科学家们正持续的研究关于抑郁症的分子机制、药物疗法、种类多样性和性别差异等。

抑郁症

其实是身体“好心办了坏事”.....

PENNY PANG

总结

如今，普遍认为抑郁症的发病机制与 HPA 的调节机制和神经递质系统的适应性机制有关，关于这些机制的假说正不断通过实验进行论证。现阶段治疗抑郁症的药物副作用极大，且适用性受到局限。要开发出更有效的抗抑郁症药物，未来的研究应充分考虑副作用，并以尊重性别差异为基础，分别对两性实验对象进行实验验证。在外界刺激来临时，HPA 就算承担着巨大的过载风险，也不轻易停止释放皮质醇，它不知道这会造成多么严重的后果，抑郁症只是它“好心办了坏事”。所以，当感觉情绪低落，孤立无援时，不妨想一想，我们的身体还在努力保护我们，去做些能让我们开心的事情，或者接受治疗，告诉身体也告诉自己：别担心，一切都会好起来的！

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机制

有关兴奋性突触的异常调节是近年来备受关注的其中一个病理机制。这一系列的反应需要从一次应激反应说起。应激反应是指释放激素和其他细胞介质的活动。当反应被适当开启或关闭时，这些介质可促进机体适应，但当反应被过度调控或失调时，这些介质也会导致系统受损。长期处于持续高应激状态将导致“下丘脑-垂体-肾上腺轴（HPA 轴）”过度激活，是抑郁症发病的关键机制 [1]。压力由大脑皮层感知，传递至下丘脑，导致 HPA 激活。HPA 活性则受下丘脑分泌的促肾上腺皮质激素释放因子（CRF）和血管加压素（AVP）的调节，而后者又会刺激垂体分泌促肾上腺皮质激素（ACTH）。最终激活肾上腺皮质分泌糖皮质激素（在人体内为皮质醇，能够调节神经元存活、神经发生、事件的情绪评估等活动，是压力和大脑功能之间的关键联系），糖皮质激素随后也与位于 HPA 轴内的受体结合，对 CRF、AVP 和 ACTH 分泌发挥反馈控制作用[2]。因此，由于抑郁症患者的 HPA 轴由于被不断激活导致“过载”，导致唾液、血浆和尿液中的皮质醇水平升高。

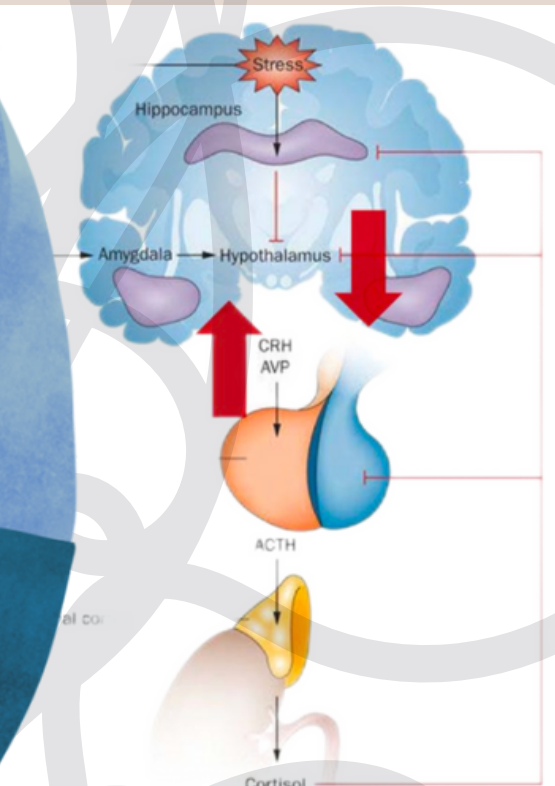


图1: HPA在压力刺激下的作用机制

如今最主流的抑郁症机制就是 HPA 轴-5-HT 这一假说，其余假说多涉及炎症反应，免疫应答，线粒体功能等方面，各种假说互为补充，共同阐释着抑郁症的复杂机制。

图2: 5-HT及去甲肾上腺素神经传导机制及药物治疗作用位点。

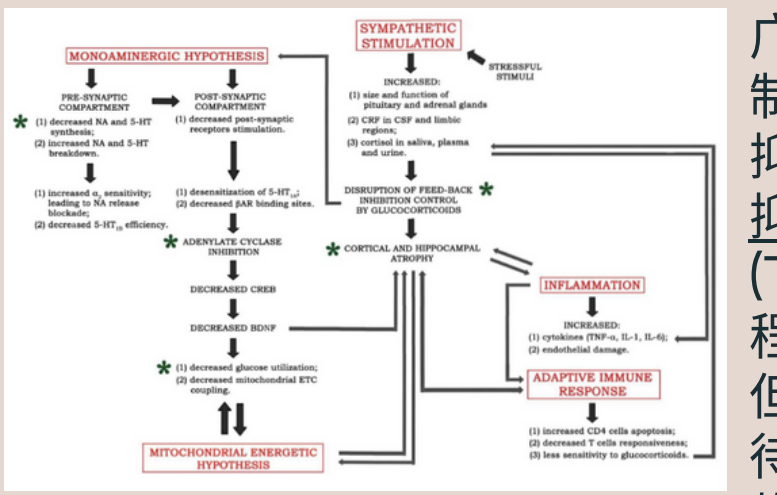
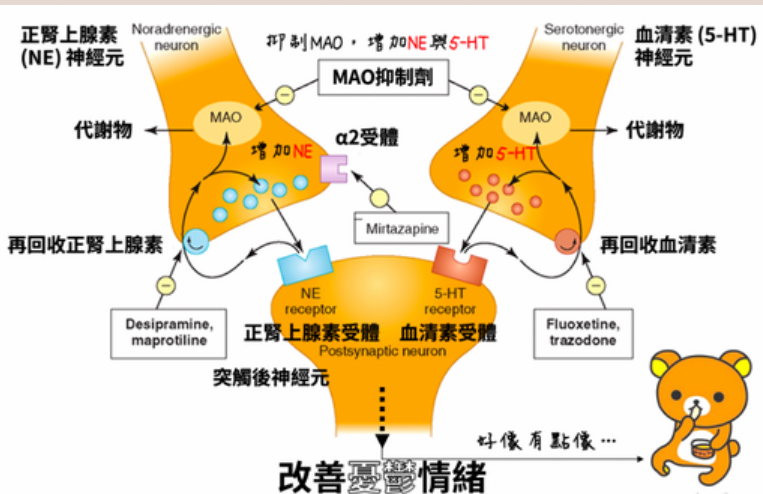


图3: 抑郁症病理生理学假说之间的相互作用 [2]

广泛使用的抗抑郁症药物主要基于抑制重吸收过程，如 5-羟色胺再摄取抑制剂(SSRI)及去甲肾上腺素再摄取抑制剂(SNRI)，杂环类抗抑郁药(TCAs)，或基于抑制激素氧化过程，如单胺氧化酶抑制剂(MAOI)。但以上药物均具有极大的副作用，急待开发高效且副作用低的精神类药物。

性别差异

纵然大体上看抑郁症的致病机制相同，但在一些重要的激素调控方面却存在着性别差异。如在 CRF 分泌过多的情况下，雄性的 LC 神经元会降低对 CRF 的反应，从而防止高水平的觉醒，降低边缘性不愉快的感受。雌性 LC 神经元对急性剂量的 CRF 更敏感，其 LC 神经元的强直性放电率在相同应激条件下是雄性的三倍，因此女性将比男性更可能经历痛觉过敏症状。又因为临床研究在过去一直以雄性啮齿动物作为实验对象，并认为雌性也应显示出同样的研究结果，导致这些差异的回路和机制尚未得到充分研究。如今，这种性别差异的忽视问题正开始得到解决。总而言之，性别差异是多种精神疾病特征分析的基础，这些发现让我们能够对大脑中各种类型的性别差异进行概念化，这反过来又使将性别视为一个生物变量有着更广泛的意义。重要的是，性别之间的比较有助于发现新的治疗方法[4]。

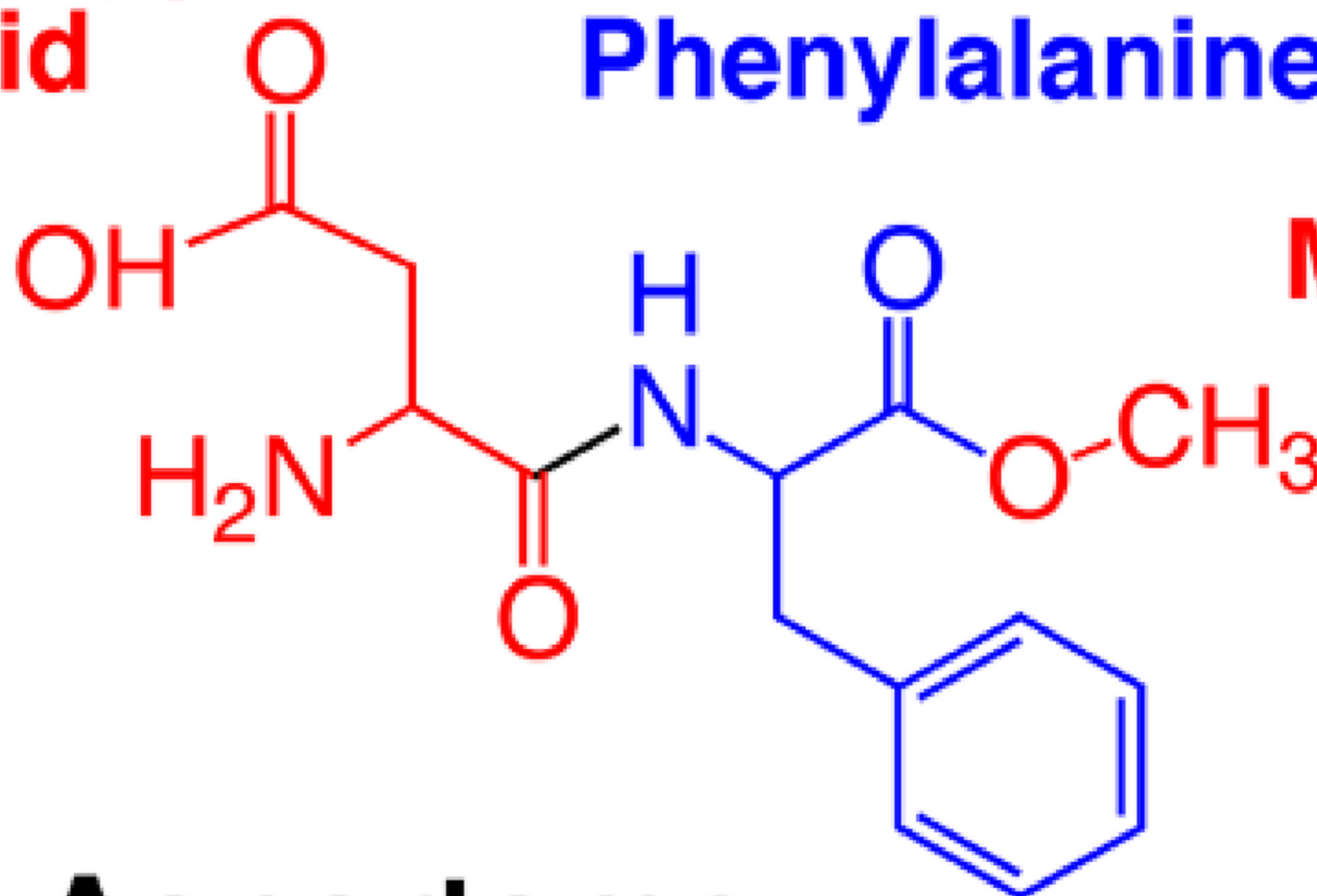
SMART MAGAZINE

人工甜味剂对人体究竟有无危害？

Aspartic
acid

Phenylalanine

Methanol



Aspartame

关键字：

人工甜味剂
蔗糖
糖尿病
胰岛素

什么是人工甜味剂？

人工甜味剂（Artificial Sweetener）是一种经过化学合成的化合物，可用于替代天然糖分或增强食品的甜味。由于其不会参与人体代谢且不产生热量，人工甜味剂比天然提取的糖类含有更少的卡路里或无卡路里，因此被广泛应用于食品和饮料工业中的低糖或无糖产品。例如，在我们生活中频繁出现的无糖汽水和无糖糕点，其实都包含了人工甜味剂。那么具体有哪些常见的人工甜味剂呢？

常见的人工甜味剂

阿斯巴甜（Aspartame）是一种非营养性甜味剂，在口感上与蔗糖相近，甜度却是蔗糖的 200 倍左右。它产生较少的卡路里，通常用于饮料、无糖或低糖食品中。

雪利糖醇（Xylitol）是一种天然糖醇，味道与蔗糖相似，但热量更低。它可用于糖果、口香糖和牙膏等产品中，还有助于预防蛀牙。

苯甲酸钠（Sodium saccharin）與糖精（Saccharin）是两种非常甜的人工甜味剂，甜度皆为蔗糖的 300-500 倍，它们通常用于饮料、糕点和药物等产品中。

安赛蜜（Acesulfame）是一种用于食品和个人护理产品的人造甜味剂。用于食品，如乳制品、甜点和烘焙产品，或用于口腔卫生用品，如牙膏和漱口水。

三氯蔗糖（Sucralose）俗称蔗糖素，是一种高倍甜味剂。其是以蔗糖为原料的功能性甜味剂，甜度可达蔗糖的 320 - 1000 倍。

这些人工甜味剂在提供甜味的同时却又不造成热量负担，对于控制糖分摄入和较低卡路里的饮食来说是有帮助的。有许多科学研究表示人工甜味剂在适度的摄入下不会对人体造成危害。然而，近年愈来愈多的研究证实了人工甜味剂的影响，说明长期过量摄入人工甜味剂也可能带来一些潜在的健康风险。那么人工甜味剂会对人体造成什么样的危害呢？

人工甜味剂的潜在风险

首先，人工甜味剂通常具有高度甜味而没有提供糖分和卡路里，这使得它们成为糖尿病患者和减肥人群的选择。然而有一些研究表明，长期大量摄入人工甜味剂可能与代谢综合征、心血管疾病和第二型糖尿病等健康问题有关。这可能是由于人工甜味剂刺激了胰岛素的分泌，从而干扰了血糖调节机制。巴黎北索邦大学研究团队于 2022 年 9 月在《英国医学杂志》发布了他们关于人工甜味剂的实验研究，结果显示人工甜味剂与心血管疾病、脑血管疾病和冠心病有着密不可分的关系。其中阿斯巴甜会增加脑血管的发病率，安赛蜜和三氯蔗糖则会增加冠心病的发病率。

其次，人工甜味剂的摄入可能会对个体的味觉产生影响。如果经常摄入高度甜味的食物或饮料，人们的味觉可能会变得偏好更甜的食物，从而导致摄入过多的糖分和能量。不仅如此，人工甜味剂会使人变得更加饥饿。悉尼大学的研究人员利用了两组分别摄入人工甜味剂和天然甜味剂的果蝇，结果表明食用人工甜味剂的一组比另一组多摄入了 30% 的能量。人工甜味剂能够暂时刺激食欲的这一特性，其影响是否有益也仍待讨论与证实。

综上所述，人工甜味剂的危害仍然是一个充满争议的问题。尽管人工甜味剂在我们生活中频繁的出现，可能会让我们放松警惕。但控制人工甜味剂的摄入还是重要且需要广泛提倡的。

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作者: ICEY

我们如何保护基因多样性并保存及利用植物遗传资源？ 关键词：遗传多样性

资源保护、遗传变异、作物改良

"遗传多样性与植物遗传资源的保护和利用"一文全面探讨了植物物种遗传多样性的关键主题 [1]。文章从学术角度出发，深入探讨了遗传变异、保护工作和植物遗传资源的实际利用之间错综复杂的相互作用。

上世纪中叶，育种计划的引入为 "绿色革命 "奠定了基础，并带来了农业产量的成倍增长。然而，这也导致了陆地品种的替代和单一种植系统的扩大。结果，75% 以上的遗传基因多样性和 90% 的作物品种从农民的田地里消失了[5]。现在，为了在气候变化、全球环境问题和人口急剧增长的情况下维持农业生产系统，"保护剩余的 PGRs 至关重要"[1]。

通过对现有文献和实证研究的深入研究，文章强调了植物遗传资源

(PGRs) 中遗传多样性的极端重要性。遗传多样性的产生是由于 DNA 核苷酸序列的遗传变异、染色体突变以及有性生殖过程中的重组。本文阐明了遗传变异如何促进植物物种的恢复力、适应力和进化潜力，从而影响它们在不同环境条件下茁壮成长和应对新挑战的能力。

有几种因素会改变植物遗传资源的遗传多样性，其中包括突变、选择、遗传漂变和基因流[2]。根据查尔斯-达尔文的进化论（1859 年），优势基因型将被选择并传给后代。随着现代栽培品种的发展，通过自然选择和人工选择都可以实现重大的基因转变。例如，植物育种者更倾向于选择具有高产、抗生物和非生物胁迫、适应性广、不破碎、种子大、早熟、品质优良等特性的作物品种[3, 4]。

身为最重要的 PGRs，粮食和农业被异地保存在基因库中，基因库的重点是作物品种间和品种内的多样性。截至 2020 年，共有 711 个基因库和 16 个区域/国际机构中心分布在 90 个国家，保存了超过 7051 个属的 540 多万份登录[6]。此外，作者还深入探讨了植物遗传资源管理的法律和伦理层面，重点介绍了旨在促进遗传资源获取、同时确保公平惠益分享的国际协定和政策。

经过保护后，植物遗传资源可用于作物改良。从杂交计划中的植物遗传资源中选取不同的亲本，至少可在 8-11 年内培育出新的作物品种[7]。此外，这些品种还可以通过加入来自野生近缘植物或野生物种的新等位基因进一步改良。这一过程涉及传统育种方法和现代植物基因工程。

这篇文章综合了遗传多样性、保护和利用的各个方面，有助于全面理解遗传资源与人类福祉之间错综复杂的关系。最后且不重要的一点是，我们期待保护和利用植物遗传资源之间的微妙平衡能够造福当代，后代以及环境。

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细胞中蛋白降解新机制

BY: Rachel

Intro

在哺乳动物中，生长因子、神经元和免疫刺激引发的转录反应是由即早期基因（IEG）介导的，而这些基因编码 Fos、EGR 和 NR4A 的转录因子家庭。IEG 蛋白在几乎所有哺乳动物细胞中都会被激活并促进晚期反应基因（LRG）的转录，这种基因对于细胞类型特异性的初始刺激反应至关重要。因此，IEG 表达异常与癌症、免疫缺陷和神经系统疾病相关。IEG mRNA 在初始刺激后短时间内积累，一旦翻译，其蛋白质迅速降解，实现蛋白质表达的瞬时爆发。尽管对 IEG 转录调控机制已有较好的了解，但多年来 IEG 蛋白迅速被特异性降解的机制仍然是未解之谜。

原理

真核细胞倚赖蛋白酶体这种大分子蛋白酶有效地降解被泛素标记的蛋白质。有学者提出，Fos 家族蛋白在进入蛋白酶体时可能既经历泛素化依赖的机制，也可能有不依赖泛素的机制，但是这些分子过程的协调依然难以明确。研究假设存在一种能够快速降解 c-Fos 和其他 IEG 蛋白的细胞通路。通过利用正向遗传筛选，研究旨在揭示控制这些蛋白质降解的机制。

结论

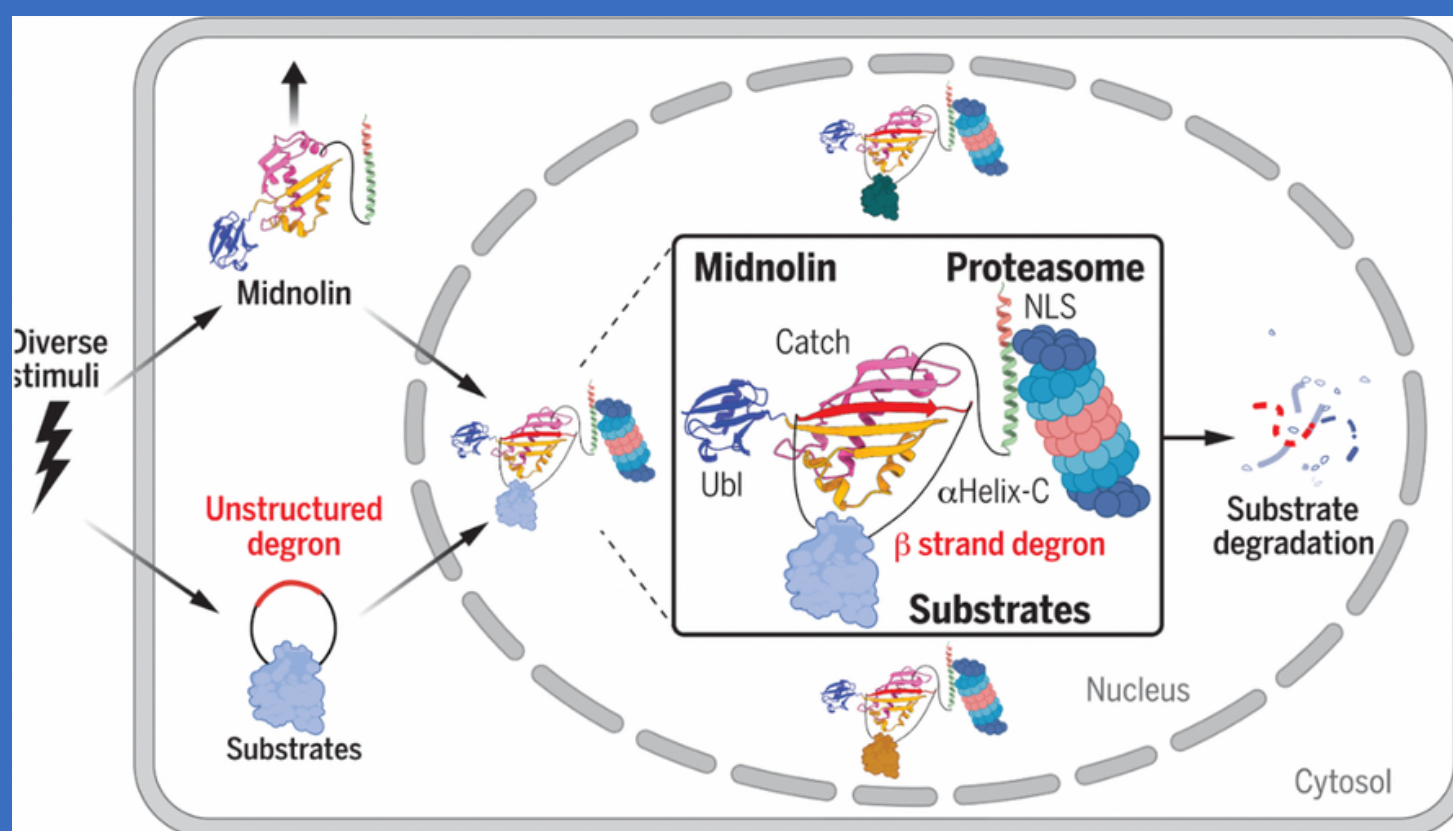
研究指出，Midnolin-蛋白酶体途径可能是一种通用机制，用于在核蛋白的选择性降解中绕过经典的泛素化系统，尤其是那些对于转录至关重要的核蛋白。Midnolin在底物内识别那些具有可能形成 β 链的简并的两性区域，因此，其降解决定子可能是许多蛋白质常见的结构组成部分。未来的研究需要探索如何通过不同细胞类型中的多种信号来调节 Midnolin-蛋白酶体途径，以控制转录程序。

引入

真核细胞内含有一种被称为蛋白酶体的大分子蛋白酶，它能够分解被泛素修饰的蛋白质，但是蛋白酶体也可以降解未被泛素修饰的蛋白质，但这个过程的具体机制目前仍不清楚。最近研究人员发现了一种名为 Midnolin 的蛋白质，它位于细胞核内，能够促进许多转录调节因子通过蛋白酶体降解，但这些转录调节因子并未被泛素。实验表明 Midnolin 与蛋白酶体紧密结合，并利用包含游离 β 链结构域的机制来“捕获”底物以进行分解。因此，Midnolin-蛋白酶体途径绕过了传统的泛素化系统，实现了对许多细胞核蛋白有选择性的降解。

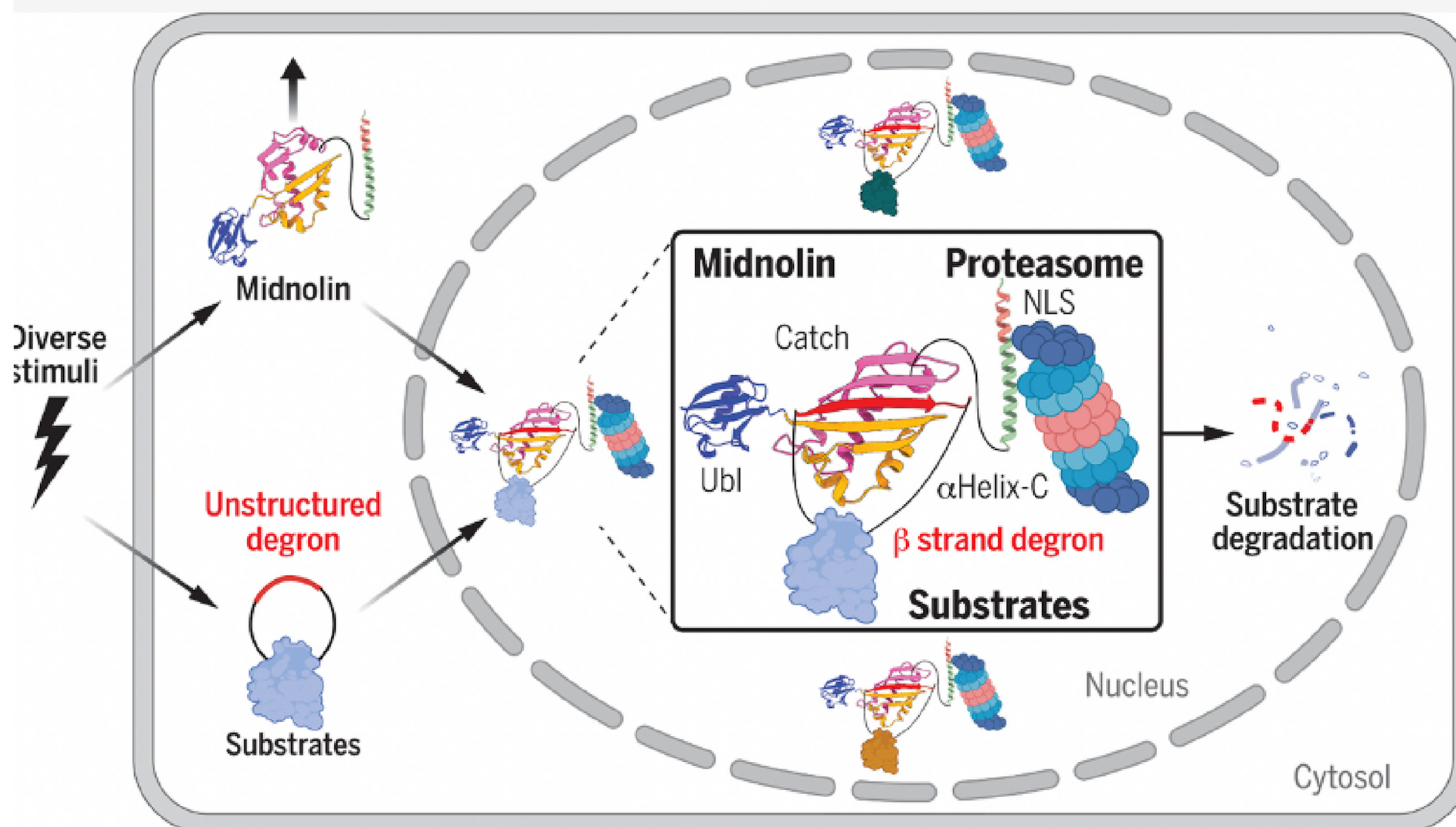
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研究采用全基因组 CRISPR-Cas9 筛选，探寻调节 IEG 蛋白稳定性的基因。结果在哺乳动物中发现了一种名为 Midnolin 的蛋白质，在 IEG 蛋白（如 c-Fos、FosB、EGR1 和 NR4A1）中促进蛋白酶体降解，而这种情况并不依赖泛素化。此外，Midnolin 也导致其他多种蛋白质的降解，包括细胞核中的特异性转录调节因子。IEG 的多种刺激也会激活 Midnolin 的表达，而过度表达 Midnolin 会引发靶标的进行不依赖泛素化的降解。此外，Midnolin 使用其“Catch”结构域来接合底物，该结构域对于与底物内的非结构化区域相互作用是必要且充分的，这些非结构化区域有可能在结合 Midnolin 时形成 β 链。此外，Midnolin 通过 C 端 α 螺旋与蛋白酶体稳定结合，并通过其 N 端泛素样结构域促进 Catch 结合靶标的降解。因此，Midnolin 包含三个保守的结构域，通过协同作用，能够将大量核蛋白直接靶向蛋白酶体，实现不依赖泛素化的降解。



SMART MAGAZINE

细胞中蛋白降解新机制



引入

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作者: RACHEL



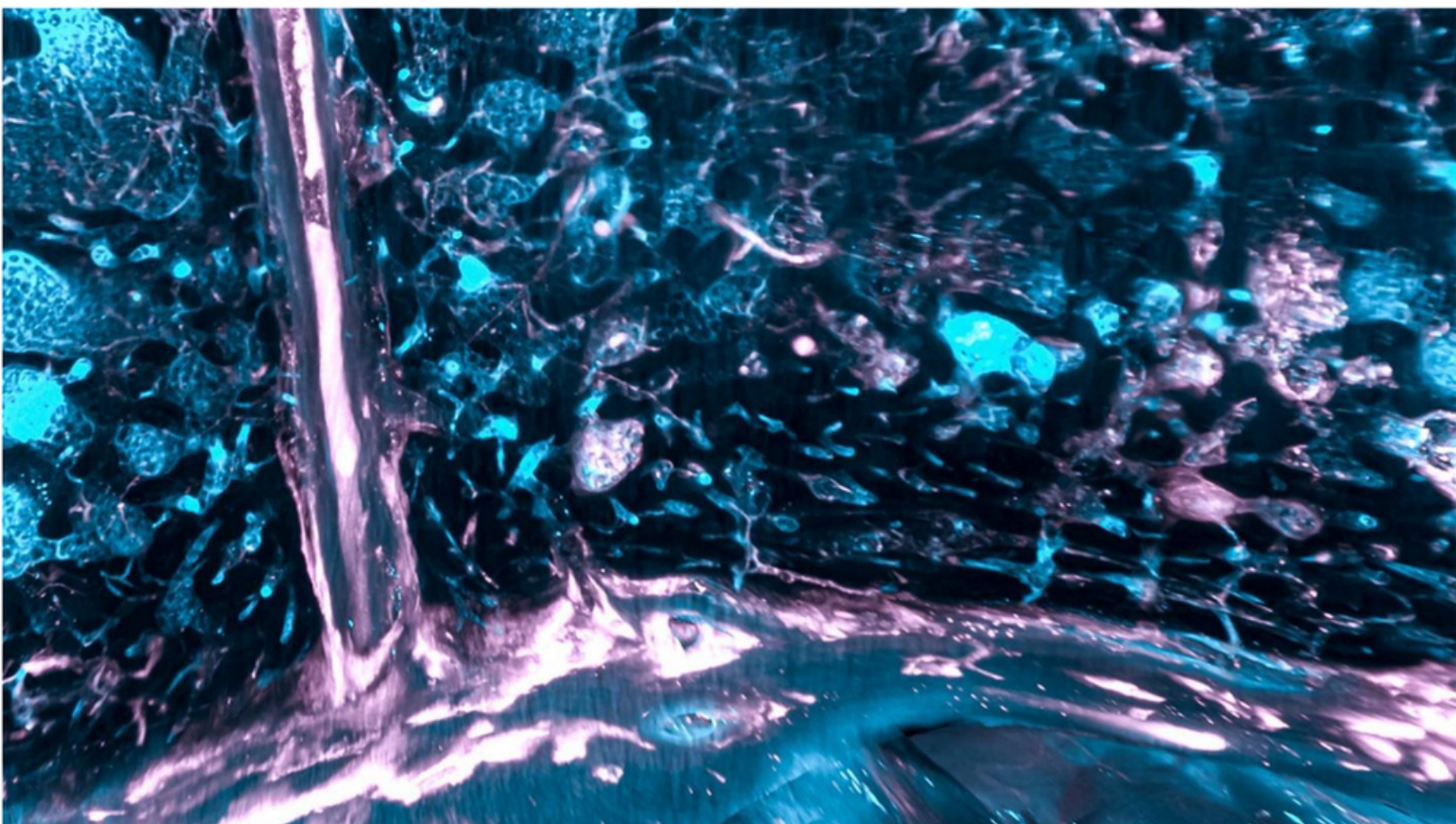
头骨里的骨髓竟然可以用 来“跟踪”神经疾病？

BY: Wei Zhang

数百年来，神经疾病一直被人们当成无药可医的不治之症。哪怕到了科技空前发达的今天，科学家们对神经疾病的了解仍然停留在症状与潜在的发病原因，对于发病的具体机理是毫无头绪。因此，能够快速诊断出精神疾病并加以治疗是神经医生的首要任务。然而，当今的临床诊断与科幻作品中扫描一通便能获得一个人的所有健康信息截然相反。例如，为了能确定患者是否罹患老年痴呆症，神经科医生往往需要从老人的脊髓中提取适量的脑脊液，再通过脑脊液中各种与老年痴呆有关之蛋白的表达水平来做出最终的诊断。毫无疑问，这一流程无疑是极为痛苦的。所以，发现并采用一种不会对病人造成过多伤害的诊断方式便成了前沿研究者的热门课题。近日，世界各地的研究者们相继发现，那些一直藏在头骨里的细胞们，竟有望帮助医生们发现大脑出现的各种炎症反应，从而对患者的病情做出初步的推断。

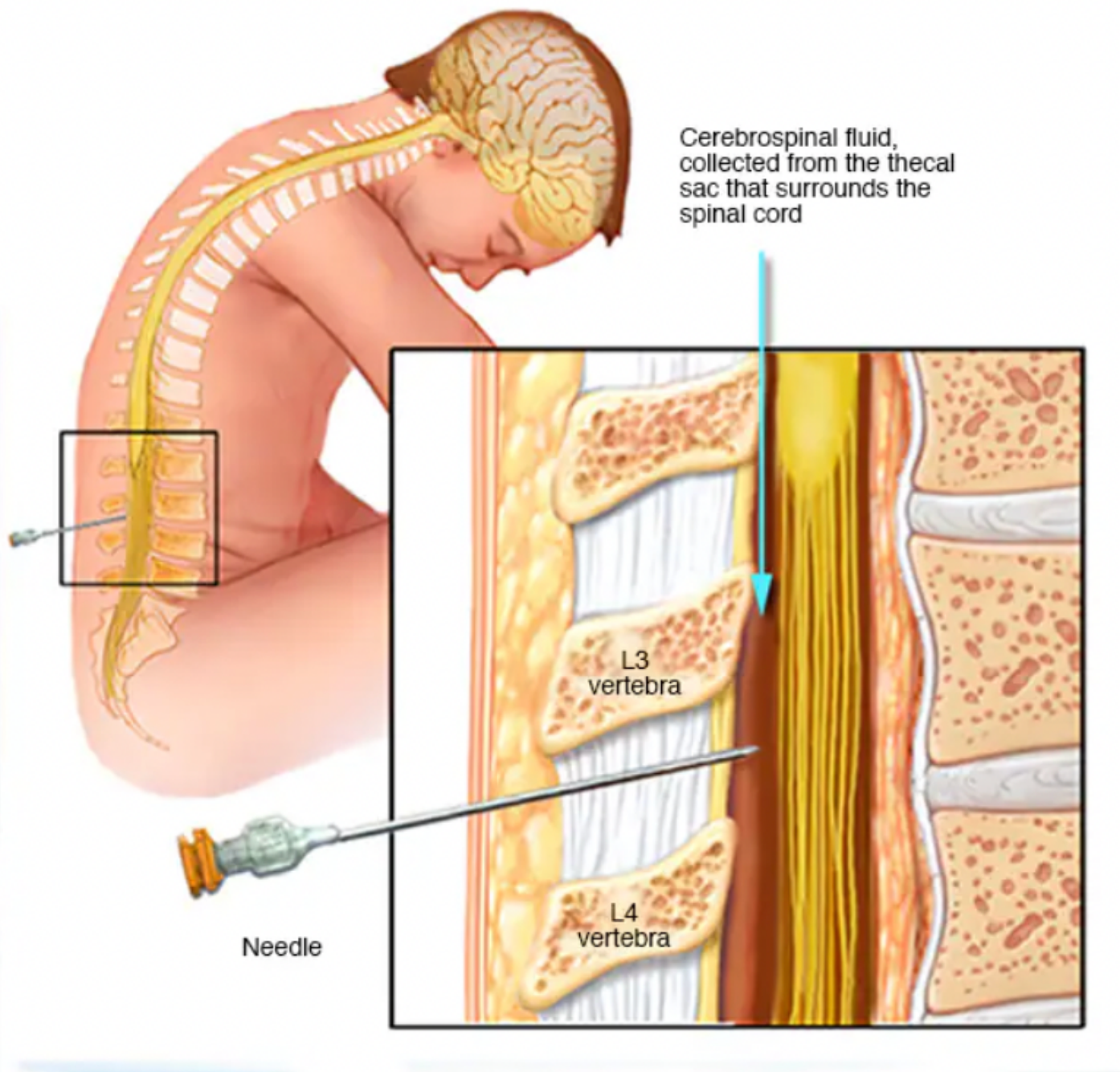
研究者们已经利用正子断层扫描（PET）追踪过老年痴呆、中风或多发性硬化症患者头骨中神经炎症的位置和程度。而他们发现每种疾病对于头骨炎症的呈现方式都有所不同。例如，多发性硬化症患者的颅底会有一个巨大的炎症信号，而中风或老年痴呆患者则没有。Ertürk 的一位同事，Işin Kolaba 也佐证了这个观点：“炎症信号的变化取决于神经疾病的性质。在老年痴呆患者头骨的特定区域，信号甚至有所增加，这可能是疾病进展的一个迹象。”

由于这些炎症信号可能反映了大脑中正在发生的情况，因此它们可以作为神经疾病的一个潜在参考物。这些发现将有助于诊断和治疗中风、老年痴呆及其他神经系统疾病。而且最重要的是，藉由炎症发生之位置来诊断疾病的方法，比上述的脊髓穿刺法或其他替代方法创伤更小。如果在不久的将来，头骨骨髓细胞真的能投入临床使用，一系列神经疾病的诊断成本将会大幅降低，为患者及其亲属降低那压得人喘不上气的医疗负担。



图二、三维成像显示，从头骨进入大脑（下方）的不仅仅是静脉（左侧粉红色结构），还有一些可将大脑外层与头骨连接起来的“小隧道”（右下方的蓝色小竖线）。

关键字：神经系统疾病、骨髓细胞、阿尔茨海默病



图一、现有的老年痴呆诊断往往依赖于脑脊液的提取，即通过判断脑脊液中淀粉样蛋白和 tau 蛋白的含量来诊断是否患有老年痴呆症。

Ali Ertürk，一名来自德国的神经科学家及其同事在研究颅骨中的骨髓细胞与其他骨髓细胞在行为上的差异时，发现了颅骨骨髓细胞会在大脑受伤后迅速分化并往大脑移动，这代表有可能对骨髓细胞行为的观测，可以间接的预测出大脑内部发生的病变。Ertürk 的研究小组比较了小鼠头盖骨骨髓细胞与鼠类肱骨、股骨和其他四块骨头中细胞的基因表达水平与表达出的蛋白质。他们发现，颅骨中的细胞，尤其是其中一种中性粒细胞（即白细胞），与其他骨骼中的细胞不同，但与脑膜（头盖骨和大脑之间的保护膜）中的细胞相似，而脑损伤则会扩大这些差异。在有中风症状的小鼠中，颅骨骨髓细胞中与细胞迁移和炎症有关之基因的表达水平，远高于其他骨细胞，这表明细胞会对大脑中发生的任何病变做出反应。

这个发现无疑是有重大意义的，但另一个谜团是头骨骨髓细胞是如何在头盖骨和大脑之间自如穿梭的？几年前，研究人员便在小鼠和人类身上观察到头骨和脑膜之间有联通的“隧道（tunnels）”，让骨髓细胞与免疫细胞能够自如地在头盖骨与大脑之间往返。因此，骨髓细胞的移动已基本被证实与大脑的损伤有显著的关系。而接下来需要关注的便是骨髓细胞对于不同神经疾病的反应。