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Artículo de investigación

Exploring food neophobia in mice: unraveling behavior and implications for laboratory research

Explorando la neofobia alimentaria en ratones: descifrando el comportamiento e implicaciones para la investigación en laboratorio

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Abstract

Food neophobia refers to avoiding foods to which the subject has not been exposed. This phenomenon influences food preference and intake. Other conditions that directly affect food consumption are inflammatory diseases such as neurological and respiratory illnesses. This study made a comparative analysis of exploratory behavior in BALB/c mice under healthy (intact control) and unhealthy conditions (i.p. lipopolysaccharide administration). Additionally, the investigation aimed to examine mice's inclination towards sweet flavors in both healthy and unhealthy states. Lastly, the study evaluated the preference for sweet and salty flavors alongside standard food in healthy mice by measuring behavioral variables such as distance traveled, average speed and frequency. Behavioral tests were performed on the mice, recorded, and analyzed with specialized software. The data were processed and analyzed, the Kolmogorov-Smirnov test and a Tukey post hoc test were performed. The results suggest that flavor perception plays a critical role in the feeding behavior of mice, particularly sweet taste ($p<0.0001$). It was found that there are anxiety-like behaviors when exposed for the first time to snacks associated with said flavor. The methodology used and the results obtained are beneficial for evaluating the function of taste in rodents since stimulus-response interactions must be considered in behavioral tests.

Keywords: neophobia, food preference, feeding behavior, animal models, taste.

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Resumen

La neofobia alimentaria se refiere a la evitación de alimentos a los que el sujeto no ha sido anteriormente expuesto. Este fenómeno influye en la preferencia e ingesta de alimento. Otras condicionantes que afectan de manera directa al consumo de alimento son las enfermedades de carácter inflamatorio tales como enfermedades neurológicas y respiratorias. Este estudio evaluó la conducta exploratoria de ratones de la cepa BALB/c bajo condiciones saludables (control intacto) y condiciones no saludables (administración i.p. de lipopolisacárido). Además, se examinó la inclinación de los ratones hacia los sabores dulces tanto en estados saludables como no saludables. Finalmente, se evaluó la preferencia por sabores dulces y salados junto a comida estándar en ratones sanos midiendo variables de comportamiento como la distancia recorrida, la velocidad media y la frecuencia. Se realizaron pruebas conductuales en los ratones, las cuales fueron grabadas y analizadas en un software especializado. Los datos fueron procesados y analizados, se realizó la prueba de Kolmogorov-Smirnov y una prueba post hoc de Tukey. Los resultados sugieren que la percepción de sabor juega un papel crítico en la conducta alimentaria de los ratones, particularmente para el sabor dulce. Se encontró que hay conductas de tipo ansiosa al ser expuestos por primera vez a los bocadillos asociados a dicho sabor. La metodología empleada y los resultados obtenidos son de gran utilidad para realizar evaluaciones de la función del gusto en roedores, ya que se deben considerar las interacciones del estímulo-respuesta en pruebas conductuales.

Palabras clave: neofobia, preferencia alimentaria, conducta alimentaria, modelos animales, sabor.

Introduction

Neophobia refers to the behavior of aversion to novelty. It should be noted that neophobia is not the same as aversion condition, which requires repeated avoidance to be classified as such (Demattè et al., 2014). However, studies have also found that animals tend to change their preferences when presented with novelty, eventually accepting it after repeated exposure (Appleton et al., 2018).

This behavior was initially studied from a comparative psychology perspective to quantify non-human fear, anxiety, curiosity, and memory. Despite that, is also commonly used in psychopharmacology and neurobiology for testing drugs and mapping brain circuitry. Currently, behavioral ecologists studied neophobic behavior, focusing instead on the adaptive value, evolutionary trade-offs, and ecological consequences of variation in neophobia across species, populations, and individuals (Greenberg & Mettke-Hofmann, 2001; Greggor et al., 2015).

The way animals, particularly mammals, interact with food is influenced by a range of factors, such as social, psychological, and biological stimuli. These factors can increase or decrease food consumption. Food neophobia is one factor that can affect feeding behavior, which refers to the avoidance of unfamiliar foods by the subject (Zajonc, 1965).

The senses of smell and taste play a vital role in determining the suitability of food for consumption. These senses enable animals to distinguish between nutritious and harmful foods and help mammals develop food preferences. Research suggests that mammals prefer sweet flavors over salty or savory ones. This is primarily due to the evolutionary association of sweet flavors with higher energy levels required for daily activities and survival. Consequently, it can be concluded that animals naturally favor foods that stimulate a sweet taste (Ventura & Worobey, 2013).

Psychologists have researched animal behavior, explicitly feeding behavior, by examining aspects such as latency, frequency, and duration (Cross & Lane, 1962; Fath et al., 1983). By measuring these variables, connections have been established between food consumption and health conditions linked to insufficient nutrition (Martínez, 2018).

Using murine models in a laboratory setting is instrumental in comprehending the intricacies associated with medication efficacy and identifying and mitigating any potential adverse effects. Additionally, it is vital to incorporate behavioral variables related to feeding within the domain of basic sciences. This is because evaluating food intake and hunger levels aids in assessing the degree of disease present in animals, thereby enabling comparisons between control, treatment, and patient groups (Guo et al., 2019).

The present study sought a comparative analysis of exploratory behavior in mice under healthy and unhealthy conditions. Additionally, the investigation aimed to examine mice's inclination towards sweet flavors in both health and unhealthy states. Lastly, the study evaluated the preference for sweet and salty flavors alongside standard food in healthy mice.

Methods

Subjects

Twenty adult male (3 to 4 months old) BALB/c mice with 20-25 g body weight were obtained from Centro de Investigación Biomédica de Occidente. Mice were kept together in groups of five and housed in 20 x 60 x 40 cm (width, length, height) polypropylene cages, with a room temperature of 23 ± 2 °C. Animals had free access to standard rodent food and water, except during behavioral tests. Two groups of subjects were formed: the healthy control group (intact) and the unhealthy group. Both groups were on a 12-hour light/dark cycle. All animal care and experimental procedures were performed following the official Mexican guidelines (NOM-062-ZOO-1999). Ethical approval was obtained from the institutional committee Centro y Uso de Animales de Laboratorio (CICUAL) of CUCEI, University of Guadalajara (CUCEI/CINV/CICUAL-06/2023).

Unhealthy mice. Lipopolysaccharide (LPS) from E.coli, serotype O111:B4 (Sigma-Aldrich, L2630) was dissolved in 0.9% saline solution (the total volume of the solution was 30 to 50 µL) and administered intraperitoneally in an increasing dose for seven consecutive days (Musaelyan et al., 2018). The initial dose of LPS was 35 µg/100 g body weight and increased by that amount daily. It is to be used as a positive control and thus mimic the behavior of a mouse in a chronic condition such as obesity, type 2 diabetes, cardiovascular diseases, among others.

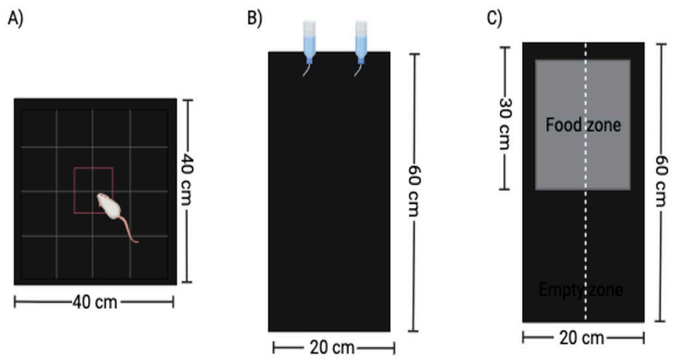

Figure 1. Description of apparatus. A) Open Field Test (OFT), B) Sucrose preference test and C) Snack preference test.

Behavioral tests

Three different behavioral tests were conducted to assess these factors under potentially unhealthy conditions. This is to understand how mice react to unfamiliar food in challenging environments. To help facilitate these tests, three distinct apparatus were utilized, each carefully designed to elicit specific responses from the test subjects. Each test lasted five minutes and apparatus were cleaned with 70% alcohol solution between subjects. Figure 1 provides a visualization of the three apparatus used for behavioral tests. The tests were recorded on video to process the data later.

Open Field Test. Open Field Test (OFT) was performed to evaluate the explorative behavior of a mouse, which is characterized by roving all the areas to which the mouse is exposed. The purpose of employing this test was to discern locomotor alterations associated with the disease. Behaviors such as distance traveled, time spent moving, time spent in the center, and activity in the first five minutes are evaluated (Gould, 2009). For this test, 20 mice were involved, and their habitual behavior patterns were analyzed.

Sucrose solution preference test. This study followed the methodology outlined by Sinclair et al. (2015), which involved assessing the preference between sucrose and water. Before the test, subjects were habituated to the experimental model over three days, with one session per day lasting an hour. On the first day, mice were placed in the experimental cage with a water bottle on the left side. On the second day, the bottle with water was placed on the right side, and on the third day, both bottles were presented in the cage, one containing a 3% sucrose solution and the other containing only water. Throughout the habituation and test days, the animals were deprived of water for eight hours beforehand.

Sweet and salty snacks preference test. The experiment tested the food preferences of healthy subjects among the control diet (pellets), sweet snacks, and salty snacks. This test was performed by offering daily 5 g of different snacks: a control snack on the first day, and on the next day, salty and sweet snacks were inter-spread. The snacks used for sweet preferences were chocolate chip cookies, chocolate sprinkles, and pieces of milk chocolate; crackers, sunflower seeds, and unsalted peanuts were used for salty preferences. The control food was the standard that the subjects were accustomed to (Purina rodent chow). The cage used in the experiment had dimensions of 20 x 60 x 40 cm (width, length, height) with a dark dividing wall in the middle, making each circuit 10 cm wide. The upper half of the cage, measuring 30 cm, was designated as the "food zone," while the lower half was labeled the "empty zone" (also 30 cm). The subjects fasted for 16 hours before the 5-minute trial, which evaluated their distance traveled, average speed, time spent in the empty area versus the food area, and latency to snack. Table 1 shows the macronutrient composition of the snacks used in this experiment.

Table 1. Macronutrient composition of sweet and salty snacks

Snack	Carbohydrates (%)	Protein (%)	Lipids (%)
Control (Pellet)	49.00	23.00	3.00
Chocolate candy lunettes	73.51	4.51	21.93
Chocolate chip cookie	67.74	6.45	15.80
Chocolate candy bar	37.00	7.50	41.00
Cracker	76.19	9.50	14.28
Sunflower seed	24.57	22.88	52.54
Peanuts	18.69	25.23	56.07

Data analysis

We employed Kolmogorov-Smirnov normality and ANOVA tests with a Fisher correction to effectively distinguish group differences. The analyzed variables were total distance, time in corners, corner frequency, time in center, frequency in center, average speed, time in empty zone, and time in food zone. The behavioral analysis was evaluated using the ANY-maze video tracking software, and the graphs were generated using GraphPad Software Inc. 9.0.0.

Results

Figure 2 compares qualitatively healthy and sick mice, illustrating that the healthy mice exhibited more movements than those induced with LPS. Moreover, the heat maps reveal that the control healthy mice were characterized by more interactions and movements than the LPS-administered sick mice.

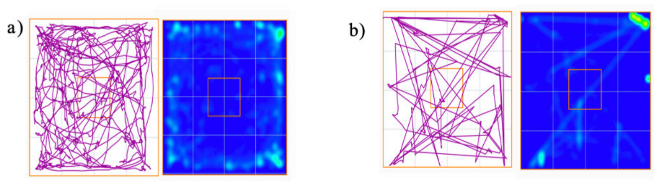

Figure 2. Track and heat map of the Open Field Test: a) healthy mice b) unhealthy mice. Left: track plot, right: heat map.

Figure 3 shows the quantitative results of the behavioral variables. In several cases, there were no significant differences between healthy and unhealthy mice. The LPS doses did not cause a noticeable change in average speed or frequency in corners. However, it can be observed that there were significant differences in the total distance traveled, time in corners, and time in the center, which could be an indicator of anxious-like behavior, characteristic of chronic inflammatory diseases.

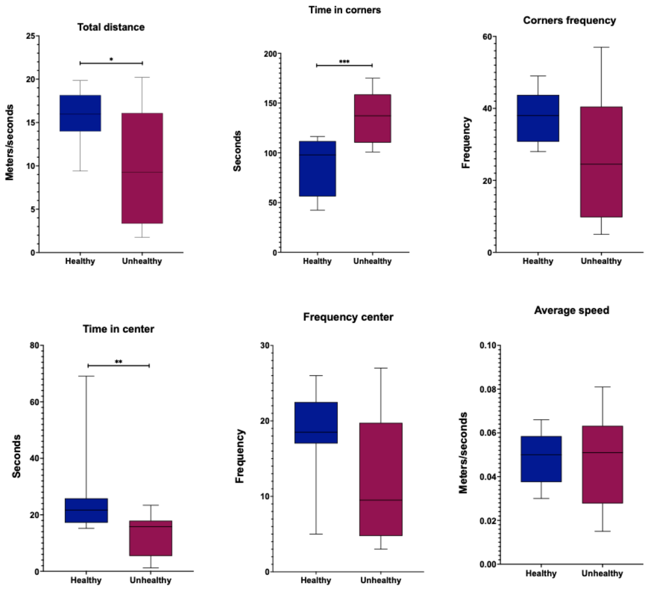

Figure 3. Behavioral variables measured in the Open Field Test. Motricity changes in open field test between control healthy mice and unhealthy mice. Blue graphs represent the healthy group, and red graphs represent the unhealthy group (n=10). Values are expressed in mean ± standard deviation; *p<0.05; **p<0.01; ***p>0.001.

According to the results depicted in Figure 4, unhealthy group subjected to chronic inflammation induced by LPS failed to differentiate between the solution containing sucrose and the one containing distilled water, in contrast to the healthy control group, which demonstrated a preference for the former.

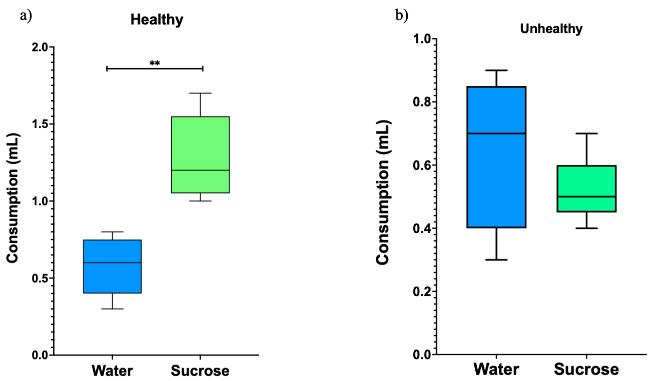

Figure 4. Comparisons of sucrose preference test. Assessment of taste function in a) healthy and b) unhealthy group (n=10). The blue bar represents the total consumption of the water solution, and the green bar indicates the total consumption of the sucrose solution. Values are expressed in mean ± standard deviation; **p<0.01.

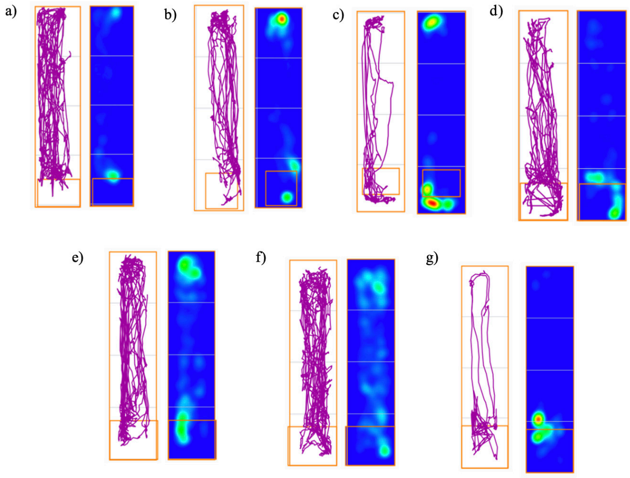

Figure 5. Track and heat map of the snack preference test. Qualitative representation of preference test: a) control, b) chocolate candy bar, c) chocolate candy lunettes, d) chocolate chip cookie, e) peanuts, f) sunflower seeds, g) crackers. Left: track plot, right: heat map.

The findings presented in Figure 5, which includes track and heat maps, indicate that sweet snacks such as chocolate candy bars, lunettes, chocolate chip cookies, and control foods tended to cause more movement and increased activity levels among mice. However, mice preferred crackers, which fall under the category of salty snacks, over the other two options, suggesting being more familiar with the other two options.

Results from this study also demonstrate that chocolate candy bars and chocolate candy lunettes affected the variables of total distance (ANOVA, F=44.16, p<0.0001) and average speed (ANOVA, F= 44.00, p<0.0001;) compared to the control (Figure 6). A high sugar content characterizes these two snacks; the rest had a very similar effect to the control food. Based on the results presented in Table 2, there was no significant difference between the preference for sweet and salty tastes. However, the study found that mice exhibited significantly different levels of distance traveled and mean speed when exposed to snacks that stimulated sweet taste.

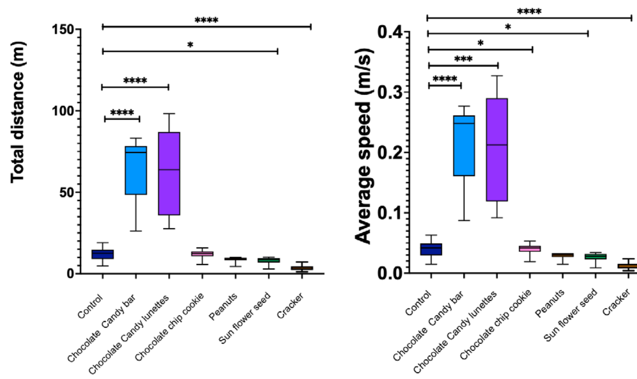

Figure 6. Changes of motricity in sweet and salty preference test. ANOVA of motor skills in sweet and salty snack preference in healthy animals (n=10). Values are expressed in mean ± standard deviation; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

Table 2. The ratio of preference between sweet and salty taste

Behavioral variable	Sweet snacks	Salty snacks	Ratio	p value
Distance travelled (m)	11.93	3.284	0.2803	<0.0001
Mean speed (m/s)	0.0399	0.0111	0.2755	<0.0001
Time in empty zone (s)	65.65	47.97	0.4256	NS
Time in food zone (s)	224.17	252.03	0.1178	NS
Latency (s)	2.999	2.059	0.1981	NS

NS: non significant; m: meters; s: seconds

Figure 7 shows that animals exposed to control food, chocolate chip cookies, and crackers spent more time in the food zone than in the empty zone; there was a significant difference between the other sweet and salty snacks. Regarding food latency, mice waited more time to make contact with control food than with other snacks, especially sunflower seeds, crackers, and peanuts.

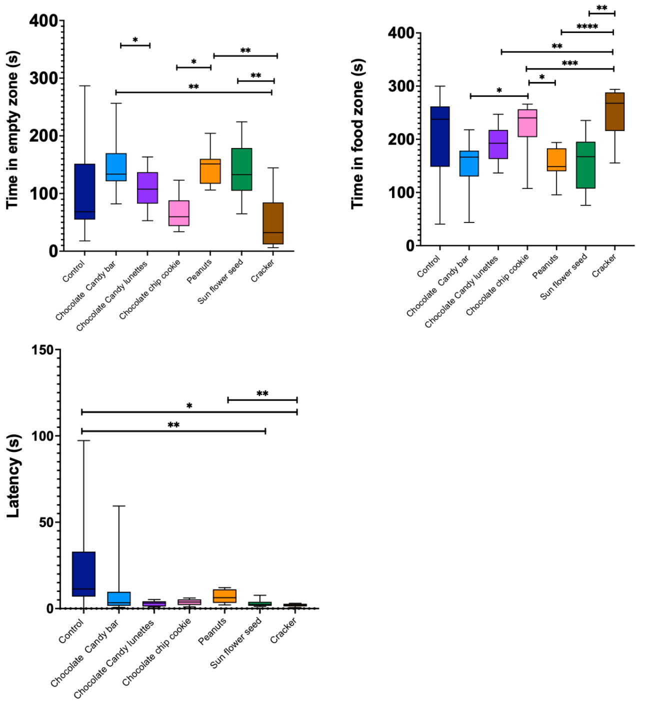

Figure 7. Sweet and salty snack preference test in healthy animals. Time spent in empty zone (seconds); Time in food zone (seconds); Latency, or time it took to the subject to make the first contact with the food (seconds).Values are expressed in mean ± standard deviation. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

Discussion

Food neophobia is studied in many fields, such as neuroscience, pharmacology, and psychology. Historical data about food neophobia were collected in animal models such as rats and monkeys, concluding that it influences food preferences and feeding behavior, which can be a useful tool to treat malnutrition and understanding this phenomenon in children (Mitchell et al., 1973; Pettus et al., 1974).

The Open Field Test assesses locomotor activity in the subjects. Conducting this test enables the identification of behavioral modifications, specifically in locomotion, attributed to a given condition or treatment. Before conducting behavioral tests, including feeding behavior, it is essential to assess locomotor activity. However, LPS administration (35 µg/100 g of weight) for seven days was insufficient to modify behavior. Despite this, anhedonic behavior was presented in the sucrose preference test and in other studies (Salazar et al., 2012; Yeh et al., 2018).

The scientific literature indicates that taste perception plays a critical role in the feeding behavior of rodents. While diseases can decrease taste perception, age-related factors can contribute to taste loss (Contri-Degiovanni et al., 2020; Narukawa et al., 2018). These tests help evaluate taste function in murine models. Recent attention has been devoted to studying taste function because its loss is a primary symptom of SARS-CoV2. Additionally, taste perception impairment is common in several chronic diseases, including obesity, type 2 diabetes, cardiovascular diseases, patients undergoing chemotherapy, and neurological diseases such as Alzheimer's and Parkinson's (Bozkurt et al., 2019; Chatindiara et al., 2020; Nigam et al., 2021; Ramos-Lopez et al., 2018; Resuli & Oktem, 2021).

Repeated consumption of sugar-rich foods has been shown to activate reward-motivation circuitry in the brain, leading to increased eating behavior. In murine models, this behavior stimulates dopamine release in cortical areas such as the nucleus accumbens (Rada et al., 2005), suggesting that food neophobia may occur upon first exposure to these foods. Our results displayed those qualitative observations (Figure 5) of anxiety-like behavior in subjects who perceive sugar-rich snacks and are supported by quantitative data (Figure 6 and Figure 7), which showed that they tend to keep a greater distance and move faster when offered sugary snacks like chocolate candy bars and chocolate candy lunettes. Additionally, mice tended to exhibit increased energy levels reflected in food consumption, particularly with increased dependence on glucose as a substrate (Carneiro-Nascimento et al., 2020).

Textures are essential to understand taste. The nervous tissue of our taste buds is responsible for detecting flavors and textures, which ultimately dictate sour food preferences (Bolhuis & Forde, 2020). This was demonstrated when the mice preferred crackers with a texture similar to control food. While these findings are intriguing, further research is needed to fully understand textures' role in taste perception.

In the case of humans, food and nutritional choices are also determined by social, spiritual, and religious aspects (De Garine, 1999). Culturally nutritional substances are classified, in the most basic way, as edible and inedible. At the same time, while for one individual, the consumption of a particular food may be accepted or seen as usual, for another it may be repudiated (Contreras & Gracia, 2005). What is accepted or rejected is the result of a complex process of biological-cultural mediation; if one adds to this the belief systems, ideologies, and psychological states, in addition to the socioeconomic and historical contexts in which we eat, the question becomes even more complex (Contreras & Gracia, 2005).

The methodology employed is beneficial in assessing taste function and the effectiveness of drugs linked to improving gustation. Nonetheless, it is crucial to consider food neophobia and environmental habituation, lighting, odors, and familiarization with the apparatus or maze used to avoid bias. Using behavioral tests in murine models is highly advantageous as it provides a range of habitual behaviors common to mammals. It facilitates analyzing stimulus-response interaction in basic science and clinical trials in psychology, nutrition, and pharmaceutics.

Conclusion

Food neophobia is a behavior that influences food preference and intake in mice. This study evaluated food preferences and found that sweet taste plays a critical role in feeding behavior in BALB/c strain mice associated with increased locomotion when exposed for the first time to snacks that stimulate sweet taste. These results help develop animal models for studying food preferences and intake in laboratory research.

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