Effects of different sweeteners on behavior and neurotransmitters release in mice

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Abstract Four natural sweeteners (sucrose, stevioside, maltose and xylitol) and six artificial sweeteners (acesulfame, sucralose, aspartame, cyclamate, saccharin and neotame) were used to study the effects of different sweeteners on the behavior and neurotransmitter release of mice with two-bottle preference experiments. The results showed that very significant preference behavior for 8% sucrose solution, 0.3% stevioside solution, 10 mM acesulfame, 10 mM sucralose and 10 mM aspartame solutions ($p < 0.01$) was observed on mice. Long-term exposure of sucrose solution and acesulfame solution can affect the behavioral indicators such as solution consumption, feed intake, body weight and the release of neurotransmitters in mice. The solution consumption and the release of neurotransmitters were significantly greater ($p < 0.05$) than that of the control group (water group), but there was no significant difference in feed intake. The acesulfame-A and acesulfame-B groups had no significant difference on the consumption of solution and feed intake, but there was significant difference in the release of neurotransmitters. The result also showed that different sweetener solutions with similar sweetness had the same effect on the neurotransmitters release, and it can be inferred that mice have an addictive behavioral characteristic to sucrose.

Keywords Sweeteners · Two-bottle preference test · Neurotransmitters · Mice

Introduction

Sweeteners are substances that can give sweetness to food and are very important food additives. Sweeteners can be divided into two major categories according to different sources, which are natural and artificial sweeteners (Mao and Song 2018). According to the level of energy, they can be divided into nutritive sweeteners and non-nutritive sweeteners. Artificial non-nutritive sweeteners only provide sweetness and do not provide calories with high intensity of sweetness (Sun and Liu 2018). More and more studies have shown that excessive intake of sugar not only results in the increase of calories but also affects human health (Nishida et al. 2004), such as diabetes, obesity and other diseases associated with metabolic syndrome (Lustig 2010). Abhilash et al. (2013) investigated the effect of long-term intake of aspartame on antioxidant defense status in the rat brain and the results indicate that long-term consumption of aspartame leads to an imbalance in the antioxidant/pro-oxidant status in the brain, mainly through the mechanism involving the glutathione-dependent system. In addition, recent research has found that sugar is also significantly abused, like tobacco and wine, which acts on the brain and gives the signal for continued ingestion (Garber and Lustig 2011), and stimulates the production of neurotransmitters such as dopamine (DA), 5-hydroxy tryptamine (5-HT), norepinephrine (NE) and epinephrine (EPI). The replacement of sugar with non-nutritive sweeteners in food can reduce caloric intake, body weight, and cardio-metabolic risk factors, and it is a controversial topic (Gardner et al. 2012). Both positive and negative

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effects of the non-nutritive sweeteners on health have been reported, such as weight loss (Peters et al. 2016), weight gain (Fowler et al. 2015), physiological and intestinal changes (Chi et al. 2018), cardiovascular disease (Duffey et al. 2012), and metabolic diseases (Liauchonak et al. 2019). Acesulfame, sucralose, aspartame, cyclamate, saccharin and neotame are the six non-nutritive sweeteners approved for use in China. These sweeteners have been widely used in food industry. Additionally, the toxic effects of non-nutritive sweeteners have also been reported. Aspartame might result in the possible brain damage due to it can promote the onset of seizures, headaches, insomnia and behavioral modifications in humans (Kuk and Brown 2016). Acesulfame has the potential toxicity effects such as chromosome aberrations in vivo in mammals (Bandyopadhyay et al. 2008). In order to obtain a better understanding of the non-nutritive sweeteners on potential health effects, the study on the intake patterns of these sweeteners is necessary.

The two-bottle preference (TBP) behavioral experiment is a way of recommending a preference experiment by the Monell Chemical Senses Center (Bachmanov et al. 2001). The principle is based on the animal's related actions to respond to taste preference and aversion. The two bottle preference experiment provides an alternative to human body volunteers for taste evaluation (Noorjahan et al. 2014), and it is also usually used in mice for the determination of the taste preference (Talukdar et al. 2016). Compared with glucose and other uncommonly used sweeteners, the natural sweeteners (sucrose, xylitol, maltose, and stevioside) and artificial sweeteners (acesulfame, aspartame, saccharin, sodium sucrose, sucralose, and neotame) were widely used in food industry in China and in the world. In this study, the effect of these sweeteners on the preference behavior of mice, and the effect of long-term exposure of natural and artificial sweeteners on behavior and neurotransmitters release of mice were studied.

Materials and methods

Animals

Totally 190 male Kunming mice with the weight of 18–22 g at 4 weeks after the birth (Hubei Provincial Center for Experimental Animal Research, Wuhan, Hubei, China) were kept in a Specific Pathogen Free (SPF) animal room at 24–26 °C and 60% relative humidity with a 12-h light/dark cycle. And the mice had ad libitum access to standard pellet diet (Wuhan Wanqian Jiaxing Bio-Technology Co., Ltd., Wuhan, China) and water. The sterilized

sawdust was replaced every 3 days, and five mice were placed in a cage. The study was performed in line with the regulation of the administration of affairs concerning experimental animals of P.R. China. The study was confirmed by the Laboratory Animal Research Center of Hubei province and the ethics committee of Huazhong Agricultural University (HZAUMO-2018-030).

Materials

Sucrose, xylitol, maltose, acesulfame, aspartame, saccharin, cyclamate, sucralose, and neotame were of analytical grade and were purchased from Shanghai Yuanye Biotechnology Co., Ltd. (Shanghai, China). Stevioside was purchased from Zhucheng Haotian Pharm Co., Ltd (Zhucheng, China). The commercial assay kits used for the determination of the contents of dopamine (DA), 5-hydroxytryptamine (5-HT), norepinephrine (NE) and epinephrine (EPI) were purchased from Shanghai Sino Best Biological Technology Co., Ltd (Shanghai, China).

Preference test for the ten sweeteners of mice

Totally 150 male mice were divided into ten groups according to their body weight, and five mice were placed in a cage. All the mice were performed for adaptive feeding for 5 days with free way to drink water using double bottle method before the experiment. The two bottles were placed side by side on one side of the cage with the same height.

The two-bottle preference (TBP) behavioral experiment was performed to study the preference test for the ten sweeteners of mice. One of the bottles was water, and the other bottle was the sweetener solution. The concentrations of the sweetener solutions were as follows: sucrose solution (0.5%, 1%, 2%, 4%, 8%, 16%, 32%), stevioside solution (0.001%, 0.003%, 0.01%, 0.03%, 0.1%, 0.3%, 1%), maltose solution (0.01, 0.1, 1, 10, 100 mM), xylitol solution (1, 3, 10, 30, 100, 300, 600 mM), acesulfame solution (0.01, 0.1, 1, 10, 100 mM), sucralose solution (0.03, 0.1, 0.3, 1, 3, 10, 30 mM), aspartame solution (0.001, 0.01, 0.1, 1, 10 mM), cyclamate solution (0.01, 0.1, 1, 10, 100 mM), saccharin solution (0.1, 1, 3, 10, 30, 100 mM), neotame solution (0.001, 0.01, 0.1, 1, 10 mM). During the experiment, each concentration of these solutions was tested for 48 h, and the consumption of the solutions in the two bottles was recorded every 48 h, and the recording was started at 10:00 am every day. The positions of the two bottles were changed with each other every 24 h in order to prevent the position preference of the mice.

Effect of sweetener exposure on body weight, feed intake, solution consumption and the release of neurotransmitters in mice

Totally 40 male mice were divided into four groups according to the body weight. Five mice were placed in a cage, and they were pre-adapted for 2 days in the specific pathogen free (SPF) animal room. The mice were fed normally and the sawdust was changed every 3 days. The four groups were as follows: control group, free drinking water; sucrose group, free drinking 8% sucrose solution; acesulfame-A group, free drinking 0.06% acesulfame solution which had the similar sweetness with 8% sucrose solution; acesulfame-B group, free drinking 10 mM acesulfame solution. All the mice in each group were kept for 30 days. The amount of the remaining feed was weighed every 2 days in order to calculate the feed intake of the mice within 2 days, and the amount of the solution and the body weight were recorded at a fixed time.

The determination of dopamine (DA), 5-hydroxytryptamine (5-HT), norepinephrine (NE) and epinephrine (EPI) in mice

After the mice were bled, they were dissected and the whole brain was taken down. The brain was frozen using liquid nitrogen and stored at -80°C . The samples were taken out until the test. The thawed brain was dissolved in 0.9% saline at the ratio of 1:9 (w/v). Then it was homogenized and centrifuged at 4000 r/min for 5 min, and the supernatant was used for the determination of the contents of the four neurotransmitters using a commercial assay kit. The samples, standards, and HRP markers were sequentially added to the coated micropores pre-coated with DA, 5-HT, NE and EPI antibodies. Then it is incubated and thoroughly washed. The substrate TMB was used for the color reaction. TMB was converted to blue under the catalysis of peroxidase and was then converted to the final yellow color by the action of an acid. The color depth was positively correlated with DA content in the sample. The absorbance (OD value) was measured at 450 nm in the microplate reader of a Thermo Scientific Multiskan GO spectrophotometer (Thermo Fisher Scientific, Finland) to calculate the content.

Data analysis

The data were expressed as mean $\pm$ standard deviation (SD). The consumption of the tested solutions, feed intake, body weight, and the contents of DA, 5-HT, NE and EPI of mice were analyzed by one-way ANOVA in SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL).

Results and discussion

Two-bottle preference test for the four natural sweeteners on mice

As shown in Fig. 1a, the consumption of sucrose solution in mice was significantly higher than that of water, indicating that mice showed preferential behavior for all the tested concentrations of sucrose solution. The consumption of sucrose solution in mice increased gradually with the increase of their concentration from 0.5 to 4%. While it decreased when the concentration was from 8 to 32%. Conversely, the consumption of water decreased gradually from 0.5 to 4% and increased from 8 to 32%. This indicated that the increase of the consumption of sucrose solution will result in the decrease of the water consumption. The mice showed extremely strong preference behavior at 4% and 8% sucrose solution, and the consumption of sucrose solution at these concentrations was significantly greater than that at other concentrations. When the sucrose concentration was 8%, the consumption of water dropped to the lowest level. The consumption of 0.5% sucrose solution was significantly greater than water ($p < 0.05$), and the difference was extremely significant at other concentrations of sucrose solution when compared with water ($p < 0.01$). It can be seen from Fig. 1b that the mice exhibited a “preference” behavior pattern in all the tested stevioside solutions at different concentrations. And the change patterns of stevioside solution and water were similar to these of sucrose solution. The consumption of 0.03% and 0.1% stevioside solution was greater than that of water ($p < 0.05$), and it was extremely greater at 0.3% concentration than water ($p < 0.01$).

The preference curve of maltose solution in Fig. 1c was different from the sucrose and stevioside solution. The mice showed no preference on the maltose solution in the range of 0.01 to 10 mM, and the consumption of maltose solution was close to that of water. While it increased significantly when the concentration of maltose solution was more than 100 mM ($p < 0.05$), and it was extremely greater than that of water ($p < 0.01$), indicating that the mice’s preference pattern for maltose solution was “indifference-preference”. The consumption of water was also the lowest at 100 mM maltose solution. The preference pattern of xylitol in mice exhibited a “preference-avoidance” behavior (Fig. 1d). When the concentration of xylitol solution was 30 mM, the consumption of maltose solution was close to that of water. When the concentration of xylitol was 600 mM, the consumption of this solution was significantly lower than that of water ($p < 0.01$).

Fig. 1 The results of two-bottle preference test on mice for four natural sweeteners. **a** Preference curve for sucrose solution; **b** Preference curve for stevioside solution; **c** Preference curve for maltose solution; **d** Preference curve for xylitol solution [the different lower-

case letters in the same row indicate significant difference ($p < 0.05$); *in the same column indicates significant difference ($p < 0.05$), **in the same column indicates very significant difference ($p < 0.01$)]

Two-bottle preference test for the six artificial sweeteners on mice

As can be seen from Fig. 2a, the mice showed “indifferent” behavior when the concentration of acesulfame solution were 0.01 mM and 0.1 mM. The consumption of this solution was gradually increased and the consumption of water was gradually decreased with the increase of the concentration. The consumption of 10 mM acesulfame was significantly greater than water, indicating that the mice showed a significant preference behavior for acesulfame at this concentration. Then the consumption of acesulfame decreased and the consumption of water increased when the concentration of this solution increased, showing “indifferent” behavioral response. And this indicated that the mice’s preference pattern for acesulfame solution had the characteristics of “indifferent-preference-indifferent”. As seen in Fig. 2b, the consumption of sucralose solution was consistently greater than water in all the tested concentrations. And it increased with the increase of the concentration of the sucralose solution from 0.03 to 10 mM, and reached to the maximum level at 10 mM. The mice

exhibited a highly preferred behavioral response for this solution at 10 mM. Adversely, the consumption of water gradually decreased from 0.03 to 3 mM and reached to the minimum level at 3 mM. In the range of 0.03 to 1 mM, the consumption of sucralose solution was significantly greater than water ($p < 0.05$), and it was extremely greater at the 3 mM and 10 mM than water ($p < 0.01$).

As shown in Fig. 2c, it can be seen that the mice had always exhibited an “avoidance” behavioral response. The consumption of water was almost the same with each other at different concentrations of aspartame. And when the concentration of aspartame solution increased to 10 mM, the consumption of this solution increased and it was significantly different from the other concentrations. This indicated that the mice exhibited a “preference” behavioral response to this concentration of aspartame solution. The preference curve of mice for cyclamate solution in Fig. 2d was similar to that of aspartame, and also exhibited an “avoidance-preference” behavioral characteristic. The consumption of water was always higher than the cyclamate solution in the concentration from 0.01 to 10 mM. But there is no significant difference on the consumption of

Fig. 2 The results of two-bottle preference test on mice for six artificial sweeteners. **a** Preference curve for acesulfame solution; **b** Preference curve for sucralose solution; **c** Preference curve for aspartame solution; **d** Preference curve for cyclamate solution; **e** Preference curve for saccharin solution; **f** Preference curve for

cyclamate solution and water at 100 mM. As seen in Fig. 2e, the mice exhibited a “preference-avoidance” behavioral characteristic to saccharin solution. The consumption of saccharin solution was higher than that of water from 0.3 to 3 mM, and it was extremely significantly lower at 30 mM and 100 mM than water ($p < 0.01$). While the mice showed a preference pattern of “indifferent-avoidance” for neotame solution in Fig. 2f.

neotame solution (the different lower-case letters in the same row indicate significant difference ($p < 0.05$); *in the same column indicates significant difference ($p < 0.05$), **in the same column indicates very significant difference ($p < 0.01$))

From the above results, it can be seen that the mice showed extremely significant preference behavior for 8% sucrose solution and 10 mM acesulfame solution ($p < 0.01$), and a good preference curve was obtained for these two sweeteners. Sucrose is a safe nutritive sweetener that has a wide range of applications in food. Acesulfame is considered to be one of the most promising sweeteners because of its low price and superior performance.

Consequently, the natural sweetener sucrose and the artificial sweetener acesulfame were used for the further study in this paper.

Effects of sucrose and acesulfame solution exposure on feed intake of mice

The changes in feed intake during the exposure of each group of mice are shown in Fig. 3. The sucrose-exposure group had a lower feed intake during the whole experiment than the water group. The reason may be that sucrose is a natural and energetic sweetener which can provide energy to the body, and this will result in the reduction of the energy from food and the decrease of feed intake. In addition, the results of the two-bottle preference test also showed that mice had obvious sweet-preference behavior, and suitable sweetness can make them in a pleasant state. Therefore, the consumption of sucrose solution was greatly increased, and the mice were often in a full state. This results in the great decrease of the desire to eat. Guo (2013) also pointed out that sucrose was an energetic sweetener, and the energy demand of mice can be provided by sucrose due to the first-stage reaction, and the food intake was not increased.

The overall trend of feed intake in the acesulfame-A group, the acesulfame-B group and the control group were similar during the whole exposure process, and the values were also similar. It can be seen that these two concentrations of acesulfame solution had no effect on the short-term feed intake of the mice. This is different from sucrose because acesulfame is a non-caloric artificial sweetener that provides sweetness to food without increasing energy (Guo 2013). Previous study has shown that long-term activation of sweet neurons can drive a sustained increase in food intake (Hamada et al. 2008). In addition, Wang et al. (2016) also pointed out that the food intake will continue to increase even eating sucralose-free foods after

continuous intake of sucralose-containing foods because of the activation of sweet neurons. Nevertheless, different result was obtained in the present study, and the main reason might be that the different subject, different type and concentration of the sweetener, and different exposure time were used in this study.

Effects of sucrose and acesulfame solution exposure on solution consumption of mice

The changes in the consumption of the sucrose or acesulfame solution in each group during the exposure are shown in Fig. 4. Compared with the water group, the solution consumption of the sucrose-exposed group was higher than that of the water group during the whole exposure process. The difference between the consumption of sucrose solution and water was significant on the 18th, 22nd, and 30th day ($p < 0.05$), and it was extremely significant on the 26th day ($p < 0.01$). During the whole exposure process, the trend of the consumption of the solution in acesulfame-A and acesulfame-B groups was similar to that of the water group, and it was always slightly higher than the water group. This indicates that mice have a strong preference for sucrose solution. Even though the sweetness of the acesulfame solution is close to that of the sucrose solution, it is far less than the consumption of the sucrose solution. De Araujo et al. (2008) found that the brain rewards the dopamine system in responding to the caloric value of sucrose, specifically, sucrose can induce the release of dopamine in the brain of mice lacking functional sweet transduction, while the non-caloric sweetener sucralose does not play such a role. Other scientists believe that sucrose may activate the brain's natural reward pathway like drugs, releasing dopamine and opioids, which will lead to sugar addiction (Avena et al. 2008). Therefore, the dependence of mice on sucrose resulted in significant

Fig. 3 Effects of sucrose and acesulfame solution exposure on feed intake of mice

Fig. 4 Effects of sucrose and acesulfame solution exposure on solution consumption of mice

increase on the consumption of the solution compared to the water group.

Effects of sucrose and acesulfame solution exposure on body weight of mice

The changes in body weight of the mice in each group during the exposure are shown in Fig. 5. The body weight of each group increased with the increase of exposure time, and the trend was very similar. The changes in body weight of the sucrose group and the acesulfame-A group were basically consistent with those of the water group, and there was no significant difference at each day ($p > 0.05$). The body weight of acesulfame-B group was always slightly lower than that of the water group after the 6th day, but no significant difference was observed ($p > 0.05$). And this may be because that the artificial sweetener can help to reduce weight (Miller and Perez 2014). While other study showed that fat is the key factor for obesity and diabetes, not excessive intake of carbohydrates or calories (Petro et al. 2004). In addition, some researchers believe that gender may also have a certain impact on body weight. Bian et al. (2017) found that the body weight of male mice exposed to acesulfame solution was significantly increased compared with the control group, while the female mice did not, and this indicates that the increase in body weight is closely related to the sex of the mouse due to the difference in physical function, intestinal flora, etc. Therefore, changes in body weight are a complex process and are not directly affected by certain single factor.

Changes of neurotransmitters in mice

Dopamine is a neurotransmitter in the brain. It is closely related to human libido and sensation. It can transmit feelings of excitement and happiness, and is also associated

Fig. 5 Effects of sucrose and acesulfame solution exposure on body weight of mice

with various addictive behaviors (Zhao et al. 2019). In fact, evidence of anatomy, neurochemistry, and functional behavior has revealed that dopamine plays an important role in addiction (Wise and Bozarth 1987). Previous study has found that mice can consume sugar solution intermittently in a violent manner, and this will result in the release of dopamine from the brain, which is similar to the addiction characteristics caused by drugs (Avena et al. 2006). As shown in Fig. 6a, the dopamine content of the sucrose group, the acesulfame-A group and the acesulfame-B group was significantly different from that of the water group ($p < 0.05$), and it was the highest in the sucrose group. It is reported that intragastric self-infusions of sugar can stimulate the intake of and preference for a flavored non-nutritive solution paired with the intragastric infusions (Zukerman et al. 2013). And mediation of this post-oral conditioning effect is partly through the activation of the brain dopamine reward circuits (Sclafani et al. 2011).

In addition, some researchers have shown that some addictive psychostimulants not only inhibit dopamine transporters, but also promote dopamine release (Seiden et al. 1993), and they can also result in an increase in 5-HT concentrations in cells (Andrews and Lucki 2001). 5-HT is a messenger that can produce pleasure, and it can affect almost all the brain activity, such as emotion regulation, energy and memory. It can be seen from Fig. 6b that the 5-HT content of the sucrose group, the acesulfame-A group and the acesulfame-B group were significantly different from those of the water group ($p < 0.05$), and it was the highest in the sucrose group. Additionally, some researchers have shown that adrenaline and norepinephrine are the same as dopamine which is catecholamine neurotransmitter, and they are also closely related to physical functions and mental stress (Wong 2006). Adrenaline is secreted by certain stimuli (such as excitement, fear, tension), which can make people breathe faster (provide a lot of oxygen), accelerate the heartbeat and blood flow, dilate the pupil, provide more energy for physical activity, and make the reaction faster. The norepinephrine was formed firstly during the biosynthesis process, and then the epinephrine was formed from norepinephrine according to further methylation of norepinephrine by the action of phenethylamine-*N*-methyltransferase. As shown in Fig. 6c, d, the contents of NE and EPI in the whole brain of the sucrose group, the acesulfame-A group and the acesulfame-B group were significantly increased compared with the water group ($p < 0.05$). The content of these two neurotransmitters in the sucrose group was the highest, followed by the acesulfame-A group and the acesulfame-B group.

It can be inferred that the consumption of sucrose and acesulfame solution can promote the release of

Fig. 6 The contents of neurotransmitters in mice (n = 10). **a** Dopamine (DA) content; **b** 5-Hydroxytryptamine (5-HT) content; **c** Norepinephrine (NE) content; **d** Epinephrine (EPI) content. The different lower-case letters indicate significant difference ($p < 0.05$)

neurotransmitters. The results also showed that there was no significant difference in the content of dopamine, 5-HT, NE and EPI between the sucrose group and the acesulfame-A group, indicating that different sweetener solutions with similar sweetness degree have the same effect on these indicators, that is, the sweetness is an important factor affecting the content of dopamine, 5-HT, NE and EPI in mice. The caloric sweeteners and non-nutritive sweeteners can be distinguished by brain even though they are perceived as similarly sweet, which might be related to post-ingestive responses associated with caloric versus non-caloric sweeteners (Burke and Small 2015).

Conclusion

Extremely significant preference behavior for 8% sucrose solution and 10 mM acesulfame solution was observed in this study. And the mice's preference pattern for these two sweetener solutions had the same characteristics of "indifferent-preference-indifferent". Long-term exposure of sucrose and acesulfame solution could affect the behavioral indicators such as consumption, feed intake, body weight and the release of neurotransmitters in mice. The solution consumption and neurotransmitter release in the sucrose group were significantly greater than that of water group, but there was no significant difference in feed intake. No significant difference on feed intake and solution consumption was observed in acesulfame-A and acesulfame-B groups, while there was significant difference in the release of neurotransmitters between these two groups. Different sweetener solutions with similar sweetness have the same effect on these indicators, and it can be inferred that

Kunming mice have an addictive behavioral characteristic to sucrose.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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