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Self-Administration of Drugs in Mouse Models of Feeding and Obesity

Rizaldy C. Zapata[1], **Dinghong Zhang**[1], **Besma Chaudry**[1], **Olivia Osborn**[1]

[1]Division of Endocrinology and Metabolism, Department of Medicine, University of California San Diego

Abstract

Preclinical studies in mice often rely on invasive protocols, such as injections or oral gavage, to deliver drugs. These stressful routes of administration have significant effects on important metabolic parameters including food intake and body weight. Although an attractive option to circumvent this is to compound the drug in rodent food or dissolve it in water, these approaches also have limitations as they are affected by drug stability at room temperature for extended periods of time, the drug's solubility in water, and that the dosing is highly dependent on timing of food or water intake. The constant availability of the drug also limits translational relevance on how drugs are administered to patients. To overcome these limitations, drugs can be mixed with highly palatable food, such as peanut butter, allowing mice to self-administer compounds. Mice reliably and reproducibly consume the drug/peanut butter pellet in a short time frame. This approach facilitates a delivery approach with minimal stress compared with an injection or gavage. This protocol demonstrates the approach of drug preparation, animal acclimatization to placebo delivery, and drug delivery. The implications of this approach are discussed in studies related to timing of drug administration and the circadian rhythm.

Introduction

The goal of this method is to deliver drugs in mice via a non-invasive, minimally stressful procedure. Preclinical studies in mice often rely on stressful, invasive routes of drug administration that can have significant impacts on metabolic parameters. For example, repetitive daily oral gavage can significantly decrease caloric intake and weight gain in mice[1]. In addition, oral gavage can be technically challenging and has the potential to cause injuries. As an alternative, mice can self-administer compounds that are mixed in their food or dissolved in their drinking water[2].However, this approach has a major limitation, which is, it relies on the natural circadian timing of food or water intake. Furthermore, drug stability or solubility in water can be major issues when chronically delivered in this way. To overcome these limitations, drugs can be mixed with highly palatable foods, such as cookie dough[3], jelly[4,5] or peanut butter[6] to encourage self-administration in mice at a specified time. This approach has the advantage of facilitating drug delivery with minimal

Corresponding Author: **Olivia Osborn**, oosborn@health.ucsd.edu.

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stress compared with an injection or daily gavage[1]. This procedure can be adapted to deliver a wide variety of drugs to mice. This protocol demonstrates the process of drug preparation, training, followed by drug delivery in highly palatable food. As an example, this method is used to administer the antipsychotic drug risperidone to C57BL6 female mice. Risperidone is well known to have potent hyperphagic and weight gain effects in patients[7] that is well modelled in rodents[6,8]. This system of administration facilitates a highly translational model that could be used to study a wide variety of drugs and their effects on pathways regulating food intake and body weight[9].

Protocol

All procedures involving animal subjects have been approved by the Institutional Animal Care and Use Committee (IACUC) at the University of California, San Diego.

1. Making the drug-peanut butter pellet

1. Calculate the amount of drug needed to make the desired dose of drug in a pellet of peanut butter and scale to the size of the batch required for an experiment. Importantly, pellets can be kept at −80 °C, depending on drug stability.
2. Pulverize the drug tablets using a mortar and pestle.
3. Weigh the calculated amount peanut butter required by placing it in a weigh boat on a tared scale.
4. Place the peanut butter over a beaker of warm water until melted.
5. Add the required amount of pulverized drug into the melted peanut and mix thoroughly.
6. Allow the drug-peanut butter mixture to cool so that it can be easily placed into the rubber molds.
7. Place the peanut butter-drug mix into a mold. The one used here is a rubber corticosterone pellet mold and creates approximately ~100 mg peanut butter pellets.
8. Repeat these steps with peanut butter alone to make placebo pellets.
9. Freeze the mold in −80 °C to allow the peanut butter to harden until use.

2. Mouse setup

1. Singly house mice in standard mouse cages. Line with highly absorbent paper bedding and enrichment, including paper towels and housing dome. This paper bedding facilitates accurate food intake measurements by allowing quantification of spilled food from feces and bedding.
2. Provide ad libitum food and water and allow the mice to acclimate to the housing for approximately 3 days.

3. Training to self-dosing of drug-peanut butter

1. Plan and select the optimum time of the day for the drug administration.
2. Fast the mice for 24 hours.
3. Take the mold out the freezer, let the rubber mold soften so that the pellets can be easily extruded out of the mold. All training can be completed using placebo control pellets.
4. Place a placebo control peanut butter pellet on the wall of the cage approximately 1.5 inches from the base. On the first day, it may take approximately 1 hour for the mouse to consume the peanut butter pellet due to novelty.
5. After the training session provide ad libitum access to food and water.
6. On the following day, place the peanut butter pellet on the wall of the cage in the same location for further training on non-fasted mice.
7. Repeat the training in fed mice for approximately 3 days. The time taken to consume the peanut butter will be less than 30 minutes by the third day of training.

4. Experiment

1. Randomize mice to treatment groups based on body weight so the groups have the same average body weight before treatment.
2. Plan to administer the peanut butter pills (treatment or placebo) to the mice at the same time they were trained to receive the peanut butter pellets.
3. Weigh the food and mouse and record the values.
4. Ensure that the peanut butter pills (treatment or placebo) are placed at the same location in the cage as established during training.
5. Continue the dosing procedure daily for the duration of the experiment.

Representative Results

In the example presented here, peanut butter was used to deliver risperidone to mice daily for 14 days.

This study shows the chronic delivery of risperidone via this method facilitates highly reproducible increase in food intake and body weight compared with control (Figure 1a,b). In addition, this delivery method results in highly consistent data compared with alternative, more stressful delivery approaches such as intraperitoneal injections (Figure 1c,d).

Discussion

When conducting this protocol, it is important to be consistent with the accuracy of the measurements of food intake and body weight and the timing of drug administration throughout the study. While this self-administration method requires a significant training

phase, this is particularly important to acclimate the mice to the novelty of the peanut butter and ensure mice consume the drug at the time given. Once established, it also offers great experimental flexibility and can be modified and adapted to deliver drugs at multiple times per day at various doses. This technique works best when mice are consuming normal chow as their main source of nutrition. When mice are fed highly palatable high fat, high sugar diets, this can make the training phase more challenging as some mice are less motivated to consume the peanut butter under these conditions and can be a limitation of this technique.

Compared with existing methods such as injections or oral gavage, this method of self-delivery of drugs causes minimal stress and results in robust and consistent data related to drug-induced effects on metabolic phenotypes including food intake and body weight. Future applications of this technique include studies into of timing of drug delivery on food intake and weight gain in the context of circadian rhythms and metabolic health[10].

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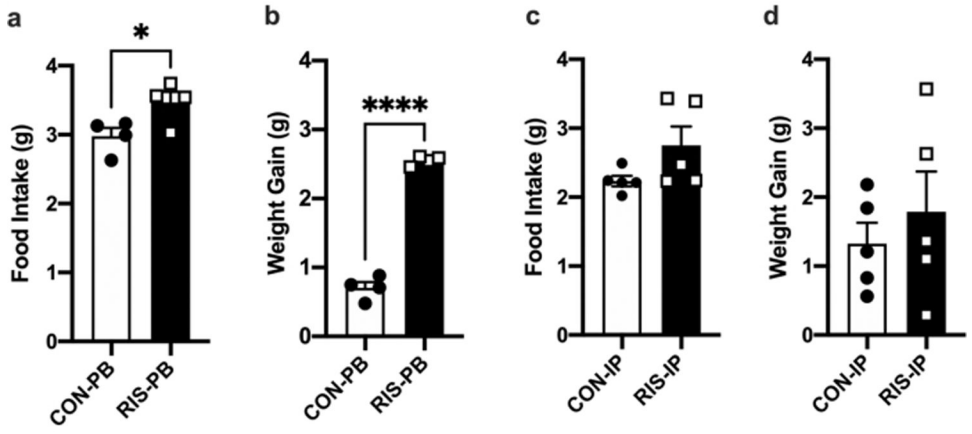

Figure 1. The effect of drug delivery methods on food intake and weight gain in mice.

C57BL6 female mice were treated with risperidone (3 mg/kg) in a peanut butter pellet or placebo control pellet daily at 8 AM for 14 days. Mice treated with risperidone in peanut butter had significantly higher daily food intake (**a**) and gained significantly more weight (**b**) compared with control treatment. Furthermore, intraperitoneal delivery of risperidone (3 mg/kg) did not have such robust effects on food intake (**c**) or weight gain (**d**) compared to self-delivery in peanut butter. Data is expressed as mean ± SEM and was analyzed by student t-test.