Brief Report

Protocol

Cocaine self-administration in the mouse: A low-cost, chronic catheter preparation

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Intravenous drug self-administration is the most valid animal model of human addiction because it allows volitional titration of the drug in the blood based on an individual's motivational state together with the pharmacokinetic properties of the drug. Here we describe a reliable low-cost mouse self-administration catheter assembly and protocol that that can be used to assess a variety of drugs of abuse with a variety of protocols. We describe a method for intravenous catheter fabrication that allows for efficient and long-lasting intravenous drug delivery. The intravenous catheters remained intact and patent for several weeks allowing us to establish stable maintenance of cocaine acquisition. This was followed by a dose response study in the same mice. For collaborators interested in premade catheters for research please make a request at www.neuro-cloud.net/nature-precedings/pomerenze.

In order to dissect the mechanisms underlying the transition from casual drug use to a state of compulsive use and dependence, effective animal models that allow the drug's pharmacokinetic profile to closely match that in humans is necessary [1]. The IV route of administration has the advantage over subcutaneous (SC) and intraperitoneal (IP) routes because it provides the rapid pharmacokinetics which is important for the rewarding properties of drugs of abuse[2]. In addition, it has been demonstrated that animals trained to self-administer cocaine exhibit long lasting neuroadaptations in excitatory synaptic strength onto ventral tegmental area (VTA) dopamine neurons after extinction training and up to 3 months of abstinence, whereas animals trained to self-administer natural rewards or given IP injections of cocaine show only transient changes in the VTA that are not resilient to extinction[3]. Furthermore, considering the amount of inbred strains, transgenic mouse lines, and genetic tools available today, the application of an IV self-administration mouse model is particularly advantageous for the integration of behavioral pharmacology with specific genetic targeting[4]. Drug self-administration in the mouse has proven notoriously difficult because of behavioral inconsistency and poor drug delivery technique. To overcome this constraint, we have designed efficient drug delivery catheters fabricated within our laboratory that remain intact and patent throughout the duration of multiple- session self-administration experiments. As a result, we have developed a self-administration setup that serves as a low- cost preparation that can be constructed easily and reliably applied to numerous acute and chronic drug self-administration paradigms.

RESULTS

Trials using the custom catheters and C57 mice yielded effective self-administration and optimal intravenous drug delivery after an average of 21.3 ± 0.97 days of retained integrity and patency. After catheterization surgery (Supplementary Methods, www.Neuro-Cloud.net/nature-precedings/pomrenzes), mice acquired the self-administration task (nose poking) and were able to maintain stable cocaine self-administration behavior for up to 5 daily 3-hour sessions while exhibiting robust discrimination to the active portal (Fig 1a/b). Catheter patency and access to the jugular vein was tested prior to acquisition using 5.0 mg/kg Sodium Brevital injections, and any animals that deviated from the normal self-administration behaviors (i.e. number of infusions per session) were examined using the same agent. Any

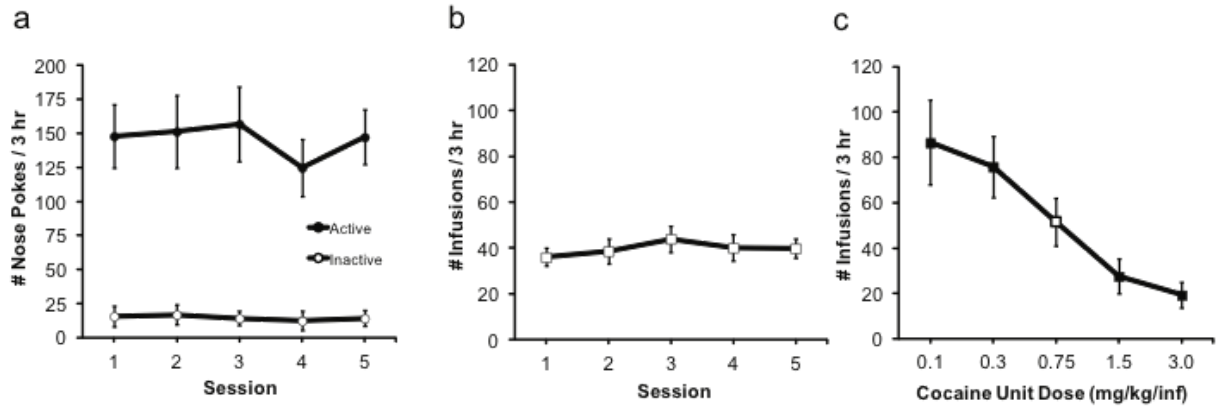

Fig. 1: Stable cocaine self-administration maintenance for 5 straight sessions. Unit dose = 0.75 mg/kg/infusion. A) Shown is the mean active vs. inactive portal responding per 3-hour session for C57 mice (n=10). B) Shown is the mean number of infusions per 3-hour session for C57 mice (n=10) C) Dose-response curve for C57 mice after 5 stable self-administration sessions (n=5). Error bars represent s.e.m.

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animals that did not exhibit rapid sedation were omitted from the trials. After stable self-administration maintenance was displayed, mice progressed to a dose-response schedule (Fig 1c). The effects of differential doses on cocaine intake reflect the successful and efficient delivery of cocaine to the jugular vein, and the behavioral sensitivity of the animals to the change in cocaine dose.

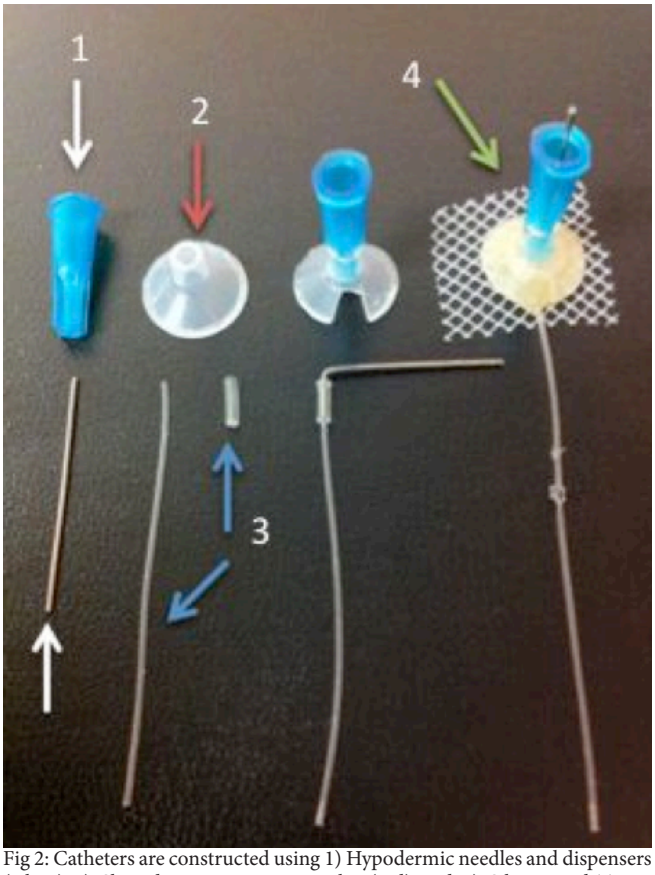

Fig 2: Catheters are constructed using 1) Hypodermic needles and dispensers (white) 2) Shaved 5 mL syringe nozzles (red) and 3) Silastic and Tygon tubing (blue) all adhered together and reinforced with cyanoacrylate cement and liquid latex mold. Nylon mesh is connected to the bottom for tissue intercalation inside the animal. 4) Completed catheter ready for implantation (green).

DISCUSSION

In light of these preliminary data, we have created a means for acquiring stable mouse drug self-administration that is cost efficient, and can be applied to various acute or chronic experimental drug paradigms. Our data show that this simple self-administration setup is capable of generating consistent behavior and reinforcement for rewarding substances. Considering the difficulties typically involved in intravenous self-administration mouse models, this setup is ideal for behavioral experiments investigating the reinforcing properties of self-administration in murine transgenic subjects. The dose-response data indicate that significant effects of different doses are attainable through the consistent and reliable delivery of the drug. This indicates that the mice were titrating the level of cocaine reward by adjusting their ongoing nose-poking behavior within the session. The basis for any drug dependence study is initial, stable responding or drug seeking behavior. Once established, experimental manipulations such as stress, conditional gene knockout, or optogenetic control of specific neural circuits can be imposed. The potentiation of VTA synapses after active cocaine intake compared to passive intake indicates that the rapid pharmacokinetics of IV delivery is an important component of cocaine addiction[3]. The IV self-administration model is thus an invaluable method for investigating drug-seeking behaviors. This self-administration preparation uses inexpensive and durable catheter supplies that can be easily assembled for successful self-administration testing. The advantages to this method include ease of use, affordable supplies for construction and reliable IV drug delivery. Our cocaine self-administration catheter procedure serves as reliable, low-cost method that is easy to integrate into any drug laboratory environment.

METHODS

The construction of the self-administration apparatus begins with assembly of the animal boxes, which contain six animal housing units each equipped with two nose-poke response portals. These are built from custom cut pieces of black acrylic adhered together using strong solvent cement with clear retracting doors attached with a plastic hinge (Supplementary Methods, www.Neuro-Cloud.net/nature-precedings/pomrenze). Beam breaks at the nose-poke operandums, each of which contain an infrared photosensor and a white LED, are reinforced with a light cue and cocaine reward in the active portal and have no consequence in the inactive portal.

Premade Custom mouse catheters can be obtained by visiting www.neuro-cloud.net/nature-precedings/pomrenze and making a request. Catheters are constructed using ordinary 23 gauge needles (Precision Glide, Becton Dickinson). Needles are extracted from the plastic dispensers and the bevels are snapped off. The nozzles of the 5mL syringes are sawed off and shaved down to be smooth and contoured. The plastic needle dispensers are shaved down as needed and inserted into the syringe nozzles so that the nozzle serves as a platform for the upright standing dispenser. After a slit is made in the base of the nozzle, the needle plumbing is bent at a right angle, adhered to Silastic tubing with a reinforcing section of Tygon tubing, and forced through the dispenser. The base of the nozzle is reinforced with superglue and filled with liquid latex to prevent any catheter leaking (Fig 2). Finalized catheters are then adhered to a square of nylon mesh on the bottom for the binding of subcutaneous tissue and a dab of silicone is applied to the exposed Silastic tubing to be used as an anchor for insertion into the jugular vein.

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PROGRESS AND COLLABORATIONS

To see up-to-date progress or if you are interested in contributing to this project visit www.neuro-cloud.net/nature-precedings/pomrenze

We are interested in establishing new collaborations in the drug self-administration field. For those interested in obtaining our customized mouse or rats sized catheters and tethers for research please visit www.neuro-cloud.net/nature-precedings/pomrenze

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