On the Measurement of Reinforcing Efficacy of Methamphetamine Using Self-Administration Procedures:

A Review and Plan for Future Directions

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Article info:
Received: 20 December 2009
First Revision: 5 April 2010
Accepted: 15 April 2010

Key words:
Self-Administration,
Methamphetamine,
Reinforcing Efficacy.

A B S T R A C T

Methamphetamine has rapidly become more prominent in Iran, which is now second most common drug behind heroin. Moreover, initiation of methamphetamine abuse is a major cause of failure of opioid treatment programs such as Methadone maintenance treatment. This calls for development of more effective treatment methods for methamphetamine addiction, and especially development of techniques for evaluating of their effectiveness in a laboratory and controlled settings. Measuring the reinforcing efficacy of a drug during the course of a treatment can provide such an evaluation, which is typically based on self-administration procedures. This article is aimed to summarize and discuss self-administration procedures that are commonly used in human research, and especially the particular value of these procedures in studying methamphetamine addiction. We also present a self-administration procedure for assessment of reinforcing efficacy of methamphetamine.

Introduction

Addiction is characterized by compulsive drug seeking and drug taking, despite its behavioral, health and social consequences (American Psychiatric Association, 2000). That is, a drug user does not refrain from behaviors that produce drug, against deleterious context and consequences of those behaviors. This property of addictive drugs is partially because they are effective reinforces, that is, they increase the likelihood of the instrumental behaviors that lead to them.

Based on this, abuse liability of a drug is directly related to its reinforcing efficacy. This implies that an effective method for pharmacological treatment of addiction should have the following properties: (1) Reduces reinforcing effects of the abused drug, (2) Does not increase reinforcing effects of other drugs that are not currently abused by the patient, and (3) Does not reduce reinforcing potency of natural rewards, so that the patient can return to a productive life. To evaluate and compare various treatment strategies from these respects, it is critical to measure the reinforcing efficacy of drug of abuse in the laboratory controlled conditions.

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Given that Methamphetamine has rapidly become more prominent in Iran, which is now second most common drug behind heroin, development of effective treatment programs for methamphetamine addiction is of prime importance. Moreover, currently, initiation of methamphetamine abuse is one of the major causes of failure in most of heroine abusers who discontinue Methadone maintenance treatment (MMT). MMT is a technique widely used by a network of about 1200 active clinics in Iran for treatment of opioid addiction. Susceptibility of patients in MMT to methamphetamine addiction is a multi-faceted phenomenon. However, two aspects are hypothesized to play prominent roles: (1) MMT causes a decrease in reinforcing efficacy of natural rewards that the patient consumes in his/her everyday life (e.g., sexual dysfunction in men receiving MMT), and (2) MMT increase the reinforcing efficacy of methamphetamine.

Focusing on the later cause, and in general, to search for a treatment for methamphetamine addiction, measuring the reinforcing strength of methamphetamine is of clinical significance. Drug self-administration (SA) methodology is widely recognized as one the major methods for assessing the reinforcing strength of a drug. In this paradigm, a subject performs a response, such as pressing a lever, which leads to administration of a certain dose of the drug (e.g., cocaine or heroin). The SA procedure has different variations; however, its key feature is the measurement of increased behavior that produces a reinforcer such as drug. Based on this measurement, the effect of a specific intervention, such as MMT, on the reinforcing potency of methamphetamine can be investigated. For example, the choice of treatment strategy after an MMT patient has started methamphetamine abuse is important from a clinical point of view. That is, the dosage of methadone should be increased? It should be decreased? Another line of maintenance should be taken? such as Buprenorphine or tincture of opioid? Or an adjuvant should be added, such as a dopamine antagonist? These questions can be answered if in experimental settings the reinforcing effects of methamphetamine be assessed during different treatment strategies.

This article is intended to summarize and discuss SA procedures that are commonly used in human research (Comer et al., 2008; Haney & Spealman, 2008; Panlilio & Steven R Goldberg, 2007), and especially the particular value of these procedures in studying methamphetamine dependence. As a result of this review, we sought to suggest an SA procedure for assessment of reinforcing efficacy of methamphetamine.

2. Drug Self-administration Procedures

The systematic study of drug SA became prevalent in 1960s, when effective methods have introduced for the use of animals in SA experiments. Derived from methods and findings developed in animal models of drug SA, over the last 15 years the techniques for research in drug SA for use in humans and in residential ward settings has been developed. However, practical difficulties are associated with experiments conducted on both humans and animals. A major concern in SA in animals is the short life span of intravenous catheter (at most few months) after insertion. This deficiency is critical due to time consuming surgery, recovery and training, especially in experiments in which animals undergo long-term drug exposure (Thomsen & Caine, 2007). In humans, the problem is largely due to extensive facilities needed for residential settings, and ethics of using of humans in SA. In this article, regarding current human and non-human resources available in INCAS, and working expertise on both healthy and addicted subjects, we focus on SA experiments in humans, and not animals.

Drug SA procedures can be divided into two classes. In the first class, the reinforcer (e.g. cocaine) is given to the subject following a specified operant behavior. For example, the response requirement can be riding a bicycle for a specified distance (Jones & Prada, 1975), or pressing a lever for a specified number of times. Fixed-ratio schedules (FR) (section 2.1), progressive schedules (PR) (section 2.2) and second order schedules (section 2.3) are in this class of procedures.

In the second class of procedures, known as choice procedures, first the subjects are given a sample dose of the drug, and then later they are asked to choose between receiving of the same dose or an alternative reinforce, such as money. This procedure has some variants, which are described in section 2.4.

2.1.Fixed-ratio Schedules

FR schedules require a subject to emit a certain number of operant responses in order to self administer a certain dose of the drug. In an FR20, for example the subject must press the space key on a computer keyboard 20 times in order to receive the drug.

The dependent variables in this schedule are typically response rates and total number of responses within an

experimental session. When these dependent variables are graphed as a function of drug dose, an inverted U-shaped relationship between drug dose and responses appears (dose-response curve). With increase in the drug dose at the falling part of the dose-response curve, its reinforcing strength increases and leads to a higher number of responses. However, at the rising part of the curve, by increase in the drug dose, behaviorally disruptive effects of the self-administrated drug (such as satiety effect) increase and causes a decrease in response rates (Bergman & Paronis, 2006). To minimize such drug pharmacological effects, usually a long time-out period is forced between subsequent injections. However, this modification, limits the total of number of drug administrations in an experimental session. In the experiments conducted on humans, due to clinical concerns (such as chance of overdose), the falling side of the curve (high doses) is not experimented.

In a PR schedule (Hodos, 1961), the number of responses necessary to access the drug increases on a trial-by trial basis within the course of a session, until no responding occurs for a period of time. For example, initially after a predetermined number of responses (e.g. 20 lever presses), the drug is delivered. Following the first drug injection, the response requirement increases systematically (e.g. the subject should emit 30 lever presses to receive the drug). The response requirement is increased in subsequent trials until a significant reduction in the rate of responding occurs (e.g. with 1000 lever presses as the response requirement, the subject does not respond any more). A breakpoint is usually characterized by the last schedule requirement completed (1000 responses), and is thought to reflect the reinforcing potency of the drug. That is, the higher the break point, the higher the reinforcing strength of the drug, and hence, it provides a means for comparing reinforcing strength of different reinforcers (Stoops, 2008).

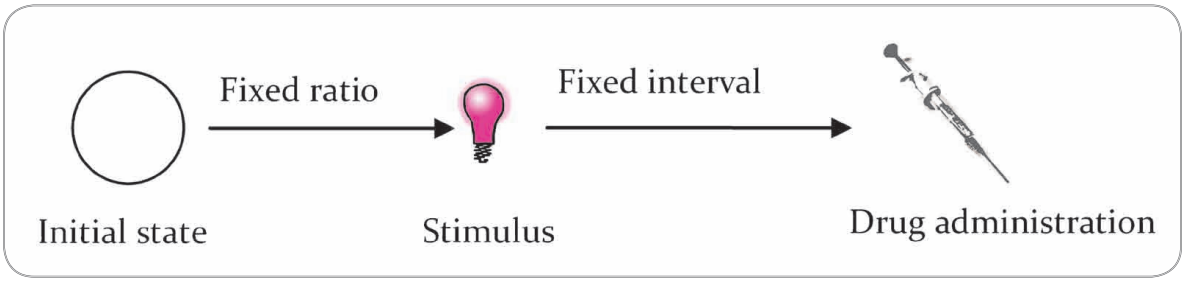

Figure 1- Second-order schedule of reinforcement. Following completion of a fixed-ratio schedule, a drug-associated stimulus is presented, & after a fixed interval lapsed, the drug is delivered.

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2.2.Progressive-ratio Schedules

In PR schedules, the breakpoint is an increasing function of the self-administered drug over a wide range of doses. That is, in this schedule, behaviorally disruptive effects of the drug are minimized, and hence, the breakpoint can provide a reliable measure for reinforcing potency of the drug.

2.3. Second-order Schedules

In second-order schedules of drug reinforcement (Everitt & Robbins, 2000), the operant behavior is maintained by a response-contingent presentation of an environmental stimulus intermittently. For example, each nth response (FRn) is accompanied by a visual stimulus that has been previously associated with a primary stimulus (e.g. cocaine). Following completion of the FRn schedule and presentation of the stimulus, after the lapse of a fixed interval (FI) the reinforcer is delivered (Figure 1).

Like PR schedules, responding under second-order schedules of reinforcement is not confounded with the drug disruptive effects. Also, this schedule is able to capture the effects of drug associated cues on drug seeking and taking are captured.

2.4. Choice SA Procedures

The effect of availability of an alternative reinforcer (drug or nondrug) on SA behavior is investigated in choice procedures. Studies of SA in humans usually use money as the alternative reinforcer. First, the subject is given a sample dose of the drug, and then (s) he is asked to choose between the sampled dose and a specific amount of money. In the subsequent trials, the amount

of money increases progressively until the subject prefers money to the drug (Donny, Bigelow, & Sharon L Walsh, 2003; Donny, Brasser, Bigelow, Stitzer, & Sharon L Walsh, 2005). The least amount of money that is preferred to the drug is regarded as a measure of reinforcing efficacy of the drug.

In another variation to the choice procedures, a combination of the availability of an alternative reinforcer and a PR schedule is used. Like the previous variant, a subject can choose between the drug and a certain amount of the money. However, after a reinforcer was chosen, the subject should complete a PR schedule in order to receive the reinforcer (Comer, Collins, & Fischman, 2001, 2002; Comer et al., 1998; Comer & Collins, 2002; Comer, Sullivan, & Walker, 2005). For example, if the money was chosen, the subject should press the space key on a computer keyboard for 200 times in order to receive the money. In the following trials, this ratio requirement increase and the subject has to complete a harder schedule to receive the reinforcer (money or drug).

The third variant of this procedure is similar to the previous variant; the only difference is that an FR schedule precedes the PR schedule (Greenwald, Kory J Schuh, Hopper, Charles R Schuster, & Chris-Ellyn Johanson, 2002; Heishman, K J Schuh, C R Schuster, Henningfield, & S R Goldberg, 2000). That is, first the subject should complete an FR schedule, after which a stimulus is presented. Following completion of this schedule, a PR starts and after its completion the reinforcer is delivered. As this variant is composed of a PR and FR, it is considered as a second-order schedule (section 2.3).

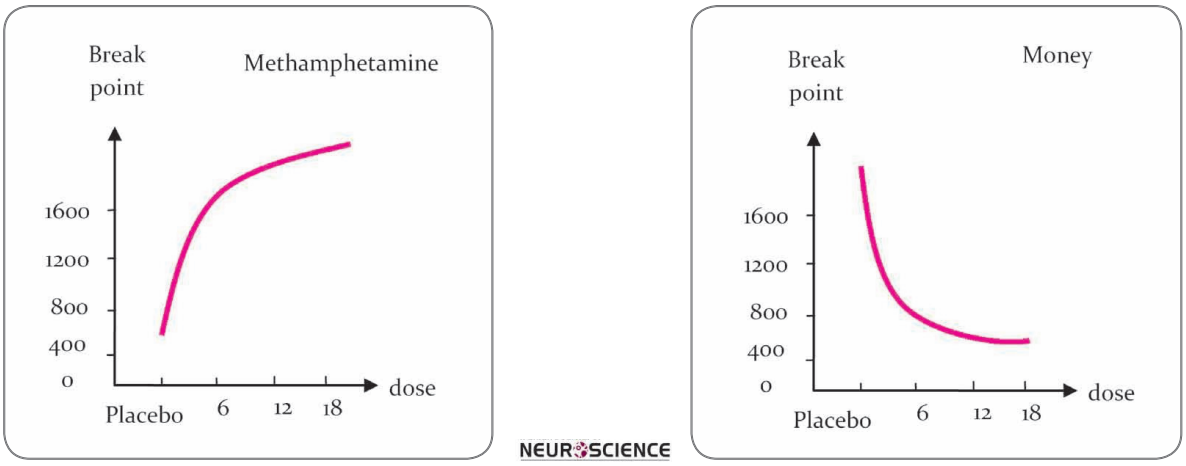

Figure 2. Progressive ratio breakpoint for the drug and money as a function of drug dose. It is expected that with increase in the drug dose, and so increase in its reinforcing strength, the breakpoint for the drug reinforcer increases, and the PR breakpoint for the alternative reinforcer (money) decreases.

3. Measuring the Reinforcing Efficacy of Methamphetamine

3.1. The Previous Work

For measuring the reinforcing potency of methamphetamine in human subjects, the previous study utilized the first variant of the choice procedure (Hart, Ward, Haney, Foltin, & Fischman, 2001). The results show that subjects reliably chose the active doses of methamphetamine over placebo, indicating that methamphetamine functions as a reinforcer. However, the reinforcing strength of the drug in the two experimented doses (10mg and 5mg) does not differ, as measured by value of the alternative choice (amount of money). This indicates that the reinforcing efficacy of the drug is not sensitive to its dose, which is an unexpected observation. As a possible explanation, the authors suggest that participants were unable to differentiate between the two doses of the drug, and perhaps if a wider range of doses be experimented, the dose-response relationship will be observed. The authors of that paper are currently working on this issue[1].

3.2. The Proposed Study

As mentioned in the previous section, at least in low doses the choice of the alternative reinforcer (1$ voucher)

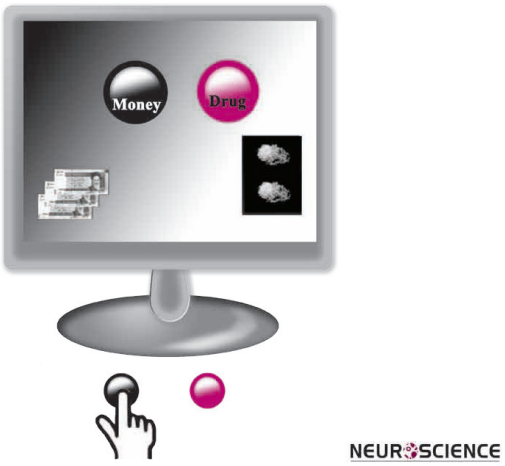

Figure 3. Illustration of the proposed task for measuring the reinforcing efficacy of methamphetamine.

is insensitive to the dose of the drug. To increase the sensitivity of the responses to the value of the drug, we suggest using the second variant of the choice task. That is, a PR should be completed before access to the drug or money. We predict that involvement of a PR to the task increases its sensitivity to the reinforcing efficacy of the drug, and hence, with an increase in the drug dose, the breakpoint of the PR schedule for methamphetamine increases, and the breakpoint of the PR schedule for the money decreases (Figure 2). The outline of the task can be as follows.

As illustrated in Figure 3, the subject has two choices, money and drug. To acquire each one, the corresponding key should be pressed for a predefined number of times. After the completion of the required response, the reinforcer appears on the computer screen. That is, if the green key was pressed for required number of times, the subject 5,000 Rials (about half a dollar). If the red key was pressed, the subject receives 10% of the daily methamphetamine dose. After the reinforcer appeared on the screen, the task restarts with an increased ratio requirement. The subjects are given ten PR schedule to choose between drug and money. The duration of the task is about 50 minutes, and after it was finished the gained reinforcers across ten trials are given to the participants.

4. Conclusion and Future Directions

Measuring reinforcing effects of drugs through the course of a treatment is a reliable method for evaluation of various treatment methods. Drug SA is an effective method for measuring the reinforcing strength of drugs. Followed from the field of operant conditioning, different methods have developed for drug SA in humans, each with its own pitfalls and benefits. In this article, we reviewed the methods that are used in humans, with a focus on measuring the reinforcing efficacy of methamphetamine. We also proposed an SA task for investigation of dose-responses relationship in methamphetamine SA.

In addition to the applications of SA methods in pharmacological intervention of drug abuse, this method can be used for assessment of other therapeutic methods. For example, the effect of brain stimulation methods and psychological interventions on the reinforcing properties of drugs can be investigated using this method. In general, development of SA methods provides a measure for assessing how well a treatment policy addresses the problem of drug abuse, which is vital in a country with growing problem of drug abuse such as Iran.

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