Measurement of Cue-Induced Craving in Human Methamphetamine-Dependent Subjects; New Methodological Hopes for Reliable Assessment of Treatment Efficacy

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ABSTRACT

Methamphetamine (MA) is a highly addictive psychostimulant drug with crucial impacts on individuals on various levels. Exposure to methamphetamine-associated cues in laboratory can elicit measureable craving and autonomic reactivity in most individuals with methamphetamine dependence and the cue reactivity can model how craving would result in continued drug seeking behaviors and relapse in real environments but study on this notion is still limited. In this brief article, the authors review studies on cue-induced craving in human methamphetamine- dependent subjects in a laboratory-based approach. Craving for methamphetamine is elicited by a variety of methods in laboratory such as paraphernalia, verbal and visual cues and imaginary scripts. In this article, we review the studies applying different cues as main methods of craving incubation in laboratory settings. The brief reviewed literature provides strong evidence that craving for methamphetamine in laboratory conditions is significantly evoked by different cues. Cue-induced craving has important treatment and clinical implications for psychotherapists and clinicians when we consider the role of induced craving in evoking intense desire or urge to use methamphetamine after or during a period of successful craving prevention program. Elicited craving for methamphetamine in laboratory conditions is significantly influenced by methamphetamine-associated cues and results in rapid craving response toward methamphetamine use. This notion can be used as a main core for laboratory-based assessment of treatment efficacy for methamphetamine-dependent patients. In addition, the laboratory settings for studying craving can bridge the gap between somehow-non-reliable preclinical animal model studies and budget demanding randomized clinical trials.

1. Introduction

Methamphetamine which is colloquially named as “meth” and “crystal meth” is a highly potent psychostimulant of the phenethylamine and amphetamine class of substances. It increases concentration, energy, alertness and in high doses, can induce elevated levels of euphoria, increase self-esteem, and sexual desire (Avram et al., 2005) (Logan, 2002). Methamphetamine is the most widely man-

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ufactured amphetamine-type stimulants (ATS) worldwide (UNODC, 2011). After cannabis, it is the most widely used illicit drug in the world (UNODC, 2011).

Methamphetamine easily stimulates the release and prevents the presynaptic reuptake of dopamine, serotonin and norepinephrine (Meredith et al., 2005) (Boles & Miotto, 2003).

Methamphetamine has a strong potential to induce dependence and an inability to remain abstinent, partly because psychostimulant drugs such as methamphetamine trigger some underlying mechanisms in brain that reinforce the basic behaviors of human survival such as sexual activity (Dickerson & Janda, 2005). No effective pharmacological treatment has been discovered to treat the disorder in methamphetamine-dependent patients until now (Rawson et al., 2002; Vocci & Appel., 2007).

In addition, craving is a serious problem in individuals diagnosed with methamphetamine dependence. Craving for an addictive substance such as methamphetamine may be described as an intense subjective urge to acquire and ingest drug, and may be induced even after periods of successful sustained abstinence by exposure to different stimuli such as visual cues previously associated with methamphetamine use (Toliver et al., 2010). Drug craving can be considered as the main core of drug abuse disorders and the main reason for referring to drugs despite a period of sustained abstinence. Assessment and measurement of different types of craving for methamphetamine in human subjects and in controlled laboratory settings are crucial targets for evaluation of treatment efficacy for methamphetamine-dependent patients. Figure1 shows how craving is evoked by a variety of cues.

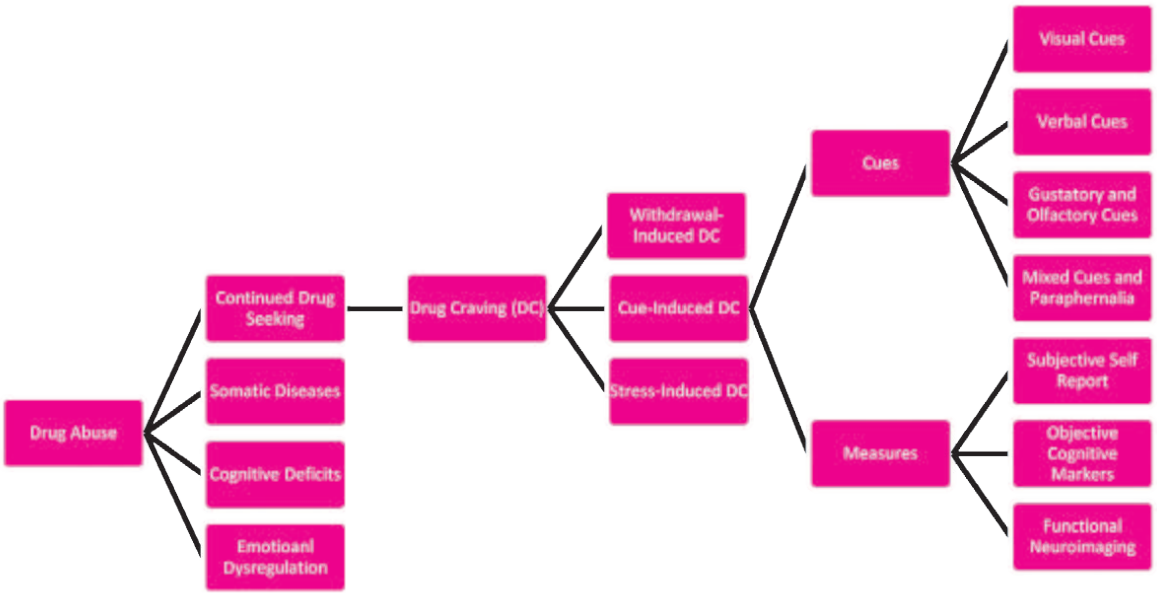

Figure 1. Different types of craving and cues associated with craving

In learning and memory models, cue-induced craving is viewed as a classical conditioning reaction in which previously neutral cues acquire incentive roles as conditioned stimuli through repeated pairings with a drug (Robinson & Berridge, 1993). Once this association is formed, exposure to the conditioned stimulus can elicit a conditioned response (craving) even in the absence of the drug (O'Brien, 2005).

Although a recent study on 420 patients enrolled in a multisite methamphetamine treatment project revealed no association of craving and subsequent methamphetamine use (Hillhouse et al., 2007) but Hartz and colleagues (2001) found that craving for methamphetamine predicts methamphetamine use in the subsequent week in dependent outpatients.

2. Cue-Induced Craving in Methamphetamine-Dependent Subjects in Laboratory Setting

In recent decades, cue-induced craving has been reported for a number of drugs of abuse including opiate (Ekhtiari et al., 2008), cocaine (Ehrman et al., 1992) and alcohol (Kaplan et al., 1985) but study on cue-induced craving related to methamphetamine use has remained in infancy while these cues have the potential to elicit

craving and have important treatment and clinical implications respectively.

In fact, study on cue-induced craving in methamphetamine-dependent patients is a new emerging field of study that is still subject to a paucity of research. Cue-induced craving has been systematically studied in laboratory settings using the cue reactivity paradigm, in which drug related cues such as videos, pictures, paraphernalia, or evocative scripts may elicit craving, autonomic arousal reactions, and activation in some brain regions (Carter & Tiffany, 1999; Childress et al., 2002) but there is a limited number of laboratory-based research studies on methamphetamine cue reactivity in human subjects (Newton et al., 2006).

Hartz and colleagues (2001) studied the role of cue-induced craving in compulsive methamphetamine use in 31 males and females in treatment for methamphetamine dependence. They asked participants to indicate craving, once each week for 12 weeks and the severity of craving that they experienced during the previous 24 h, using a visual analog scale of craving. In prospective, repeated measures, within-subject analysis, they found craving intensity was significantly predictive of methamphetamine use in the week immediately following each craving report and remained as an important predictor in multivariate models controlling for pharmacological treatment, and for methamphetamine use during the prior week. They concluded that, when craving was measured in a well planned-designed study, it can predict continued methamphetamine use for methamphetamine-dependent patients in treatment.

Newton and colleagues (2006) assessed the effects of bupropion treatment on craving induced by exposure to videotaped methamphetamine cues on 20 participants (n=10 placebo and n=10 bupropion) and showed that bupropion treatment was associated with reduced ratings of “any drug effect”, and “high” following methamphetamine administration. They also found a significant bupropion-by-cue exposure interaction on General Craving Scale total score, and on the Behavioral Intention subscale. Their study findings indicated that bupropion reduced acute methamphetamine-induced subjective effects and reduced cue-induced craving in the subjects.

Recently, Price and colleagues (2010) have examined the relationship between drug-related cue reactivity and response extinction in methamphetamine-dependent subjects in a laboratory setting. They found that methamphetamine cue-induced craving was extinguished during two sessions of repeated within-session exposures to picture, video, and in-vivo cues, without recovery between sessions. In this study, a trend was observed for a greater attenuation of response in subjects with longer (4-7 day) inter-session intervals. The results of this study revealed that extinction of drug cue conditioned responding occurred in methamphetamine-dependent persons and could be promising for the development of extinction-based treatment programs.

In addition, Tolliver and colleagues (2010) studied determinants of cue-induced craving and physiologic reactivity in 43 subjects with methamphetamine dependence by using photo, video, and paraphernalia cues and assessed the association of cue reactivity with demographic and clinical characteristics including duration, frequency, amount, and recency of methamphetamine use.

Their study findings showed that craving was reported by fewer than half of subjects at baseline and by 70% of subjects after methamphetamine cue exposure showing the role of cue-induced craving in increasing baseline craving in the subjects. Relative to baseline, researchers found that subjective craving was increased by all three cue modalities to a similar extent but physiological cue reactivity correlated poorly with cue induced craving and craving at baseline significantly predicted cue-induced craving. Furthermore, they showed that differences in cue-induced craving were not associated with demographics such as age, gender, education status, job, treatment status, or number of days using methamphetamine in the 60 days prior to study entry, but the degree of baseline craving was crucially associated with job status and the number of days using methamphetamine in the past 60 days. Their study findings indicated that cue-induced craving for methamphetamine could be measured in methamphetamine dependent cases in laboratory.

Craving for methamphetamine induced in an online virtual reality (VR) environment is a new emerging field in studies related to craving. Recently, Culbertson and colleagues (2010) have used VR drug cue model as a new model to study cue-induced craving. They assessed self-reported craving and physiological reactivity in a methamphetamine virtual reality (methamphetamine-VR) cue model created using Second life, a freely available online gaming platform. They recruited 17 non-treatment seeking persons that abused methamphetamine completed this 1-day, outpatient, within-subjects study. In this study, subjects completed 4 test sessions including 1) methamphetamine-VR, 2) neutral-VR,

3) methamphetamine-video, and 4) neutral-video and the subjects provided subjective ratings of urges to use methamphetamine, mood, and physical state throughout each cue presentation in the study. Researchers also measured heart rate during each cue presentation and at rest. Their study findings revealed that methamphetamine-VR condition elicited the greatest change in subjective reports of "crave methamphetamine", "desire methamphetamine", and "want methamphetamine" at all time points. Researchers found that "high craving" subjects displayed more high frequency cardiovascular activity while the "low craving" subjects displayed more low frequency cardiovascular activity during the cue conditions, with the most level of difference seen during the methamphetamine-VR and methamphetamine-video cues. Their study findings showed the usefulness of VR cues for inducing craving in methamphetamine abusers, as well as the effectiveness of VR drug cue model.

In Translational research methamphetamine addiction conference held by Medical University of South Carolina, USA, Brady (2010) reported data from 2 studies investigating the response of methamphetamine-dependent individuals to cues related to methamphetamine use. She reported a recent research study on measuring attentional bias towards methamphetamine-related cues. In this study, upon exposure to methamphetamine cues, rates of both response errors and inhibition errors increased dramatically in methamphetamine dependent participants. Researchers found that response error rates during methamphetamine cue exposure, but not inhibition error rates or reaction times, were significantly associated with baseline and active cue craving scores in methamphetamine- dependent subjects in the study. 24 participants in this study completed two sessions of 3 cue exposures and the researchers found that there was a crucial decrease in craving from 4.03 ± 0.65 following Sequence 1 to 0.85 ± 0.35 following Sequence 6 ($F(1,49)= 24.75$, $p<0.001$). They also reported decreases in subjective craving response between the first and third sequences of exposures within each session and between the average subjective craving response on days 1 and 3.

In another study, the majority of participants had a positive craving response to the methamphetamine cues, which was consistent with other studies on a number of abused drugs. In this study, craving at baseline strongly predicted cue-induced craving. The degree of baseline craving was higher in male participants and was strongly associated with job status and the number of days using methamphetamine in the past 60 days but differences in cue-induced craving were not correlated with some demographics such as age, treatment status, or number of days using methamphetamine in the 60 days prior to study entry.

In a review study on instruments measuring drug craving in Iran, seven main local instruments for measuring craving were defined including self-report, reinforcement "proxies", drug self-administration, psycho-physiological responding, neurobiological responding, cognitive processing and expressive behavior respectively (Maarefvand et al., 2011).

Study on cue-induced craving in methamphetamine-dependent subjects is also scarce in Iran. Recently, one study has been conducted to identify verbal cues associated with craving for methamphetamine smoking in Iran (Ekhtiari et al., 2010a). In this study, in 5 sessions, 15 active methamphetamine-dependent participants identified verbal cues that induced intense craving for methamphetamine use in them. A list of 133 cues was obtained including 133 cues in 7 clusters. Then 30 patients rated the intensity of craving that each cue evoked in them. The results of this study indicated that the words methamphetamine, substance, money, glass tube, wallet, pipe, lighter, foil, place of MA buying, deserved house, room of MA use, visiting friends, family struggle, sexual arousal, craving, anger, depression and MA dealer were the most evocative cues respectively.

In addition, a study has been recently conducted on visual cue-induced craving related to methamphetamine smoking in human subjects (Ekhtiari, et al., 2010b). In this study, an ecologically validated visual cue-induced craving assessment task was designed and evaluated for chronic Iranian methamphetamine smokers. In this study, 50 methamphetamine-dependent subjects were recruited to rate the intensity of their craving for methamphetamine to 10 neutral photos and 50 photos related to methamphetamine smoking on a visual analogue scale (VAS). The study findings revealed that the photos in the category of methamphetamine use procedure elicited intense craving and photos in the category of cues associated with drug use elicited low intensity of craving but differences in cue-induced craving were not associated with age, education, income, marital status, job status and sexual activity in the past 30 days prior to study entry but living condition was marginally associated with higher scores in the task and onset ages of opioids use, cocaine use and methamphetamine use and age of the first opiate use were negatively associated with reporting craving.

3. Discussion

Methamphetamine use is increasing as a crucial public health problem in Iran while craving for methamphetamine use and substantially attempt to prevent relapse has remained as a problem without a definite solution. This article presents a preliminary review of human laboratory-based studies with a particular emphasis on cue-induced craving elicited by different cues related to methamphetamine use in human subjects.

The common characteristic of the studies reported in this article is the focus on the role of cues associated with methamphetamine use in eliciting craving with particular emphasis on cue-reactivity paradigm in laboratory settings and the role it may have for abstinence and treatment implications.

It is apparent from these studies that there is a paucity of research in this field especially when we consider the importance of craving elicited in exposure to cues associated with methamphetamine use in relapse after success in treatment programs.

Based on these data, it is argued that methamphetamine-related cues cause significant impacts associated with exposure to these cues which in turn contribute to a number of observed behavioral changes associated with chronic abuse of methamphetamine.

Clinical lore dictates that cue-induced craving elicits the compulsive use of methamphetamine as the core feature of methamphetamine dependence. Yet limited research has yielded results, suggesting that cue-induced craving in methamphetamine users could act as a significant predictor for continued use or relapse to addictive methamphetamine. In fact, the ability of drug-related environmental cues to elicit drug craving and relapse has been systematically examined in studies related to human laboratory settings. In these settings, participants are exposed to cues related to drugs of abuse and responses are recorded but there are relatively a few studies focused on craving and cue reactivity in response to methamphetamine cues in human cases (Brady, 2010) while cue reactivity has important implications for the development of new treatment programs for methamphetamine dependence (O'Brien et al., 1992; Vocci and Appel, 2007; Conklin and Tiffany, 2002) therefore, it is important to characterize methamphetamine cue reactivity specifically.

Hopefully, laboratory-based assessment of cue-induced craving is bridging the gap between preclinical animal studies and randomized clinical trials. Human laboratory settings for studying craving may reduce the cost of clinical studies, minimize the discrepancy between animal and human studies in the development of addiction treatment, and provide controlled settings for researchers to measure higher cortical cognitive functions that are hard to be studied in animal models of craving. Next steps for the development of human laboratory settings emphasize reliable and controlled measurement of craving including (1) Instrumental development such as effective stimuli datasets, accurate response recording hardwares, and different stimuli presentation paradigms. In addition, (2) Validation including statistical power of these human-based laboratory assessments in relation to preclinical animal studies and randomized clinical trials should be clarified. (3) Recruiting more paradigms for eliciting craving assessment other than just self-reports, such as cognitive markers (i.e. attentional bias or impairments), and (4) Making links with other human-based settings such as human self-administration paradigms, neuroimaging studies, neurocognitive assessments and genetics and epigenetic studies are necessitated.

Further studies are still needed to investigate different aspects of cue-induced craving in methamphetamine- dependent individuals which may contribute to treatment of craving in these patients. Although several treatment approaches have been suggested to reduce the negative effects of craving such as cue exposure therapy (CET) which may act as a promising therapy for the treatment of craving and addictive behaviors (Drummond et al., 1995; Conklin & Tiffany, 2002) but further study on cue-induced craving is suggested to explore the effects that this notion could bring to treatment approaches.

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