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Relationship between discriminative stimulus effects and plasma methamphetamine and amphetamine levels of intramuscular methamphetamine in male rhesus monkeys

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ABSTRACT

Methamphetamine is a globally abused drug that is metabolized to amphetamine, which also produces abuse-related behavioral effects. However, the contributing role of methamphetamine metabolism to amphetamine in methamphetamine's abuse-related subjective effects is unknown. This preclinical study was designed to determine 1) the relationship between plasma methamphetamine levels and methamphetamine discriminative stimulus effects and 2) the contribution of the methamphetamine metabolite amphetamine in the discriminative stimulus effects of methamphetamine in rhesus monkeys. Adult male rhesus monkeys (n = 3) were trained to discriminate 0.18 mg/kg intramuscular (+)-methamphetamine from saline in a two-key food-reinforced discrimination procedure. Time course of saline, (+)-methamphetamine (0.032–0.32 mg/kg), and (+)-amphetamine (0.032–0.32 mg/kg) discriminative stimulus effects were determined. Parallel pharmacokinetic studies were conducted in the same monkeys to determine plasma methamphetamine and amphetamine levels after methamphetamine administration and amphetamine levels after amphetamine administration for correlation with behavior in the discrimination procedure. Both methamphetamine and amphetamine produced full, ≥90%, methamphetamine-like discriminative stimulus effects. Amphetamine displayed a slightly, but significantly, longer duration of action than methamphetamine in the discrimination procedure. Both methamphetamine and amphetamine behavioral effects were related to methamphetamine and amphetamine plasma levels by a clockwise hysteresis loop indicating acute tolerance had developed to the discriminative stimulus effects. Furthermore, amphetamine levels after methamphetamine administration were absent when methamphetamine stimulus effects were greatest and peaked when methamphetamine discriminative stimulus effects returned to saline-like levels. Overall, these results demonstrate the methamphetamine metabolite amphetamine does not contribute to methamphetamine's abuse-related subjective effects.

1. Introduction

According to the most recent 2014 World Drug Report published by the United Nations Office on Drugs and Crime, methamphetamine accounted for 80% of all amphetamine-type stimulant seizures (UNODC, 2014). Furthermore, the 2014 United States National Forensic Laboratory Information System midyear report estimates that methamphetamine ranks second behind cannabis/THC and above cocaine in both number and percentage of total drugs submitted for analysis (Drug Enforcement Administration, 2014). These epidemiological result support public health concerns regarding the prevalence and significance of methamphetamine abuse and addiction. Moreover, these epidemiological results suggest a need for preclinical studies to improve our mechanistic understanding of methamphetamine abuse-related effects.

Using positron emission tomography in humans, ^{11}C-(+)-methamphetamine uptake and clearance from the central nervous system was examined (Fowler et al., 2008). Furthermore, this time course of radiolabeled methamphetamine correlated with the time course of verbal 'high' reports after methamphetamine administration suggesting that methamphetamine uptake into the central nervous system is responsible for the abuse-related subjective effects (Newton et al., 2006). Consistent with these imaging results, plasma methamphetamine levels also correlate with methamphetamine subjective effects in humans (Cook et al., 1993). Overall, these human results suggest that plasma methamphetamine levels are the primary mediator of methamphetamine's abuse-related behavioral effects. However, methamphetamine is metabolized to amphetamine, another known abused

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drug, in humans (Cook et al., 1993; Huestis and Cone, 2007) and the degree to which amphetamine levels might contribute to methamphetamine's abuse-related behavioral effects is unknown.

Preclinical drug discrimination procedures are hypothesized to model the subjective-like drug effects in humans (Fischman and Foltin, 1991; Schuster and Johanson, 1988). Although the use of preclinical drug discrimination procedures appears to be diminishing (McMahon, 2015), these procedures are particularly useful, compared to drug self-administration procedures, for understanding the relationship between abuse-related behavioral effects as a consequence of changing plasma drug levels (Banks et al., 2013, 2015; Lamas et al., 1995). For example, a clockwise hysteresis loop related plasma cocaine levels and cocaine discriminative stimulus effects suggesting cocaine levels were the primary mediator of the behavioral effects (Lamas et al., 1995). In contrast, a counter-clockwise hysteresis loop related plasma amphetamine levels and cocaine-like discriminative stimulus effects after lisdexamfetamine administration suggesting that amphetamine, and not lisdexamfetamine, levels were the primary mediator of the behavioral effects (Banks et al., 2015). Given that methamphetamine is metabolized to amphetamine, the degree to which methamphetamine or amphetamine levels contribute to the methamphetamine discriminative stimulus effects remains to be empirically determined.

The present study was designed to address two main aims. The first aim was to ascertain, using a reverse translational approach, whether plasma methamphetamine levels correlated with methamphetamine discriminative stimulus effects in a preclinical model of human subjective-like effects. If preclinical discrimination procedures were predictive of human subjective drug effects, then we would predict a concordant behavioral and pharmacokinetic relationship. However, this hypothesis has not been directly tested for methamphetamine. A second aim was also to determine whether the methamphetamine metabolite amphetamine contributed to the methamphetamine discriminative stimulus effects. To the best of our knowledge, there are no human or preclinical studies that have determined the role of the methamphetamine metabolite amphetamine in methamphetamine-induced behavioral effects. If methamphetamine metabolism to amphetamine contributed to or mediated the discriminative stimulus effects of methamphetamine in rhesus monkeys, we would predict a counter-clockwise hysteresis loop (Louizos et al., 2014) between methamphetamine-like discriminative stimulus effects and amphetamine plasma levels similar to a counter-clockwise hysteresis loop between cocaine-like discriminative stimulus effects and amphetamine plasma levels after lisdexamfetamine administration (Banks et al., 2015).

2. Methods

2.1. Subjects

Three adult male rhesus monkeys (*Macaca mulatta*) weighing between 6 and 11 kg served as research subjects. Two monkeys (M1510 and M1511) were experimental naïve at the start of methamphetamine discrimination training and one monkey (M1479) had a

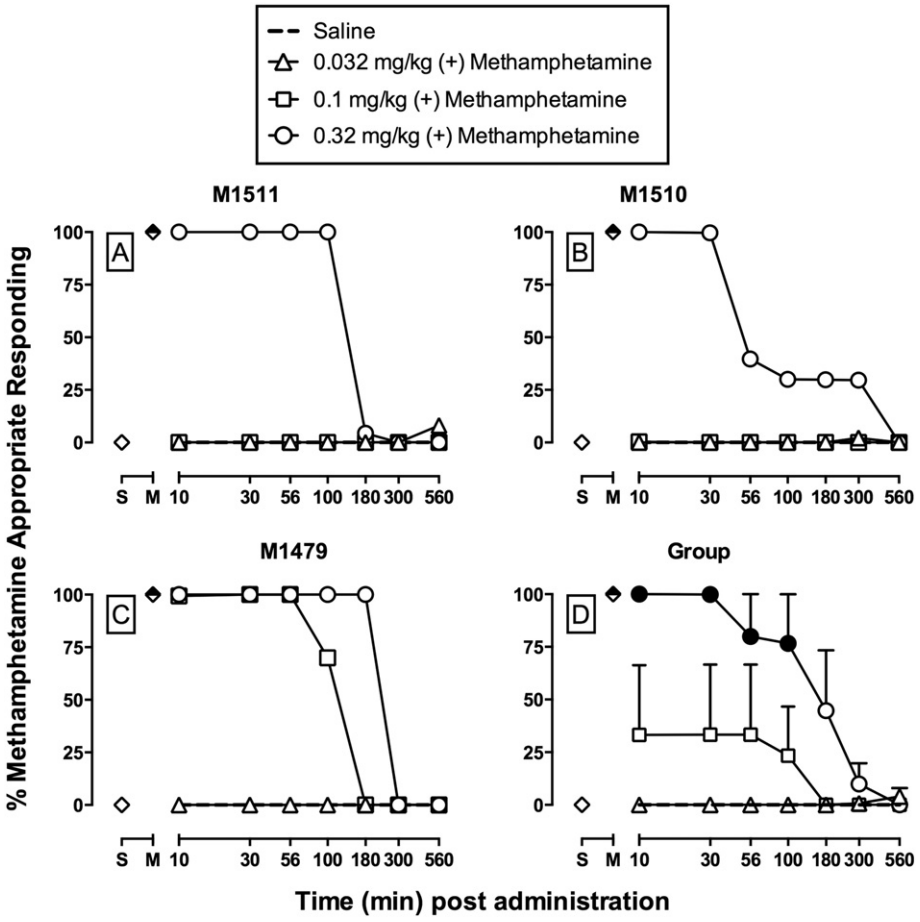

Fig. 1. Potency and time course of the discriminative stimulus effects of (+)-methamphetamine (0.032–0.32 mg/kg, IM) in rhesus monkeys (n = 3) trained to discrimination methamphetamine (0.18 mg/kg, IM) from saline. Top ordinates: percent methamphetamine-appropriate responding. Bottom ordinates: rates of responding in responses per second. Abscissae: time in min after injection (log scale). Symbols above "S" and "M" represent the averages for all training sessions preceding test sessions when the saline- and methamphetamine-associated keys were correct, respectively.