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Research Report

Methamphetamine self-administration and the effect of contingency on monoamine and metabolite tissue levels in the rat

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ABSTRACT

A number of studies have shown that exposure to high doses of methamphetamine (MA) is toxic to central dopamine (DA) and serotonin (5-HT) neurons. In most of those studies, however, high doses of MA were experimenter-administered during a short exposure time. Because contingency is a determinant for many effects of drug exposure, the present objective was to investigate the effects of self-administered MA on tissue monoamine levels following a short (24 hours) or longer (7 days) withdrawal period. As previously reported, a noncontingent "binge" high-dose treatment regimen (4 injections of 10 mg/kg MA administered every 2 hours) produced persistent depletion of cortical 5-HT and striatal DA. Effects of self-administered MA (0.1 mg/kg/infusion) were then determined following a 20-day duration where a yoked design was employed such that some rats received MA contingent on an operant lever press and others received either MA or saline dependent on the responses of the contingent rat. Self-administered MA produced a transient striatal DA depletion with a more persistent increase in DA turnover, indicating the presence of some lasting adaptations. Furthermore, the yoked design revealed that there was no effect of contingency on these parameters.

1. Introduction

The escalating use of methamphetamine (MA) relates to the relative ease of production (Lineberry and Bostwick, 2006; UNODC, 2007; Wilkins et al., 2005), multiple modes for administration (Cho, 1990), and the highly addictive properties of the drug (Romanelli and Smith, 2006). The powerful reinforcing effects of MA have been attributed to the drug's high affinity for the dopamine (DAT), norepinephrine, and serotonin (SERT) transporters (Han and Gu, 2006; Wang and Woolverton, 2007) and subsequent elevation in synaptic monoamine levels (Baumann et al., 2002; Gough et al., 2002). Of concern, high dose or repeated exposure to MA has produced damaged dopaminergic and serotonergic terminals and neuronal apoptosis (Eisch et al., 1998; Herring et al., 2008; O'Dell and Marshall, 2005; Pubill et al., 2003; Ricaurte et al., 1982; Sharma and Kiyatkin, 2008), which might underlie some of the adverse neurologic effects (Cadet et al., 2007) and

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cognitive deficits (McCann et al., 2008) frequently observed in MA abusers.

Administration of high doses of MA to laboratory animals resulted in extensive dopamine (DA) and serotonin (5-HT) depletions and decreased tyrosine hydroxylase (TH) (Kogan et al., 1976) activity across several brain regions (Quinton and Yamamoto, 2006). The striatum was especially susceptible to MA-produced depletions of DA and metabolites (Chu et al., 2008; Fitzmaurice et al., 2006; Ricaurte et al., 1984; Thomas et al., 2009; Wagner et al., 1980). High-dose MA administration also reduced 5-HT levels in the frontal cortex and hippocampus (Graham et al., 2008; Herring et al., 2008).

Depletions of monoamines were persistent and apparent at 24 hours (Pubill et al., 2003), 3 days (Broening et al., 2005; Herring et al., 2008), 1 week (Quinton and Yamamoto, 2006; Wallace et al., 1999), 3 weeks (Chapman et al., 2001), and 7 weeks (Friedman et al., 1998) following the last MA injection and were accompanied by increased glial fibrillary acid protein levels (Herring et al., 2008), peroxidative damage, apoptosis (Tokunaga et al., 2008), and decreased DA and 5-HT reuptake transporter binding (Bortolato et al., 2009), suggesting extensive neurotoxicity.

The typical exposure regimen for producing neurotoxic effects comprises 4 injections of 10 mg/kg MA, administered every 2 hours to rats, a regimen that does not reflect the pattern of exposure of MA users (Cho et al., 2001). Several other exposure methods have, therefore, attempted to more adequately model MA abuse, including chronic exposure via osmotic minipumps (Davidson et al., 2005), escalating dosing procedures (Cadet et al., 2009; Graham et al., 2008; O'Neil et al., 2006; Segal and Kuczenski, 1999; Segal et al., 2003), intravenous self-administration (Schwendt et al., 2009; Shepard et al., 2006; Stefanski et al., 1999, 2002, 2004), and pharmacokinetic modeling (Cho et al., 2001; Herring et al., 2008).

Escalating dosing regimens and pharmacokinetic modeling provide accurate approximations of the doses and patterns that humans might use but both require that MA be administered non-contingently by the experimenter. Several studies have suggested that effects of drug exposure are dependent on contingency and that differential neuroadaptations are produced when the drug is self-administered rather than passively administered (Dworkin et al., 1995; Jacobs et al., 2003; Stefanski et al., 1999, 2002, 2004).

The effect of contingency can be assessed using a yoked self-administration procedure in which one rat performs an operant task to obtain a drug infusion and another yoked rat receives the same amount of drug exposure dependent on the performance of the contingent rat. Indeed, when compared to yoked controls, rats that received MA contingently had decreased presynaptic D_2-like DA receptor densities in the ventral tegmental area (VTA) and substantia nigra (SN) 24 hours following the final drug exposure (Stefanski et al., 1999, 2002, 2004). Since these receptor alterations occurred in the absence of any change to DA transporter (DAT) binding and TH levels, it was concluded that self-administered MA had not produced a loss of DA neurons or terminal damage. In contrast to the persistent deficits produced by high-dose "binge" exposures, these deficits were not apparent 7 or 30 days following the 25 daily self-administration sessions.

Self-administration methods vary greatly across laboratories, and it has been suggested that long-duration sessions more accurately reflect patterns of human drug use (Kitamura et al., 2006; Rogers et al., 2008; Wee et al., 2007). Two more recent MA self-administration studies utilized similar procedures to Stefanski et al. (1999), except daily self-administration sessions were 9 hours (Shepard et al., 2006) or 6 hours (Schwendt et al., 2009) in duration. These animals were exposed to higher doses of MA over a shorter time period than in the experiments of Stefanski et al. (1999), but there was no effect of MA self-administration on DAT mRNA or TH protein levels in the VTA or SN and no effect on striatal and prefrontal 5-HT or DA tissue levels (Schwendt et al., 2009). The only persistent changes observed were decreases in DAT densities in the striatum and prefrontal cortex, with no changes in markers for neurotoxicity in these regions (Schwendt et al., 2009).

These findings are consistent with the idea that MA self-administration does not produce extensive neurochemical deficits and/or neurotoxicity. However, monoamine tissue levels were only assessed 14 days following the final MA self-administration session (Schwendt et al., 2009). Since most chronic dosing regimens have assessed tissue monoamine levels at earlier times following the final MA exposure, most frequently at 24 hours (Danaceau et al., 2007; Graham et al., 2008; O'Neil et al., 2006; Shepard et al., 2006; Stefanski et al., 1999), sacrifice 24 hours following the final MA self-administration session will enable comparisons across studies. This would also reveal monoamine tissue changes produced by MA self-administration over time to better understand the sequence of neuroadaptations and/or alterations in monoaminergic regulation and their recovery.

Thus, the first aim of the present study was to assess the effect of self-administered MA on monoamine and metabolite tissue levels in the striatum and frontal cortex following short (24 hours) and long (7 days) withdrawal periods to determine whether any changes were persistent. We also include an experiment replicating previous work to show that a neurotoxic MA dosing regimen (10 mg/kg every 2 hours, for a total of 4 injections) produces substantial and persistent deficits in monoamine tissue levels (Broening et al., 2005; Chapman et al., 2001; Herring et al., 2008; Pubill et al., 2003; Quinton and Yamamoto, 2006; Sonsalla and Heikkila, 1988). The second objective was to determine whether contingency could influence MA-produced neurochemical effects. To these ends, the present study utilized a yoked MA self-administration procedure that was identical to the methods used by Stefanski et al. (1999), except extended 6 hours of self-administration sessions were conducted to better mimic unlimited drug access.

2. Results

2.1. *Self-administration behavior*

2.1.1. *Effect of session time*

The effect of session time was first investigated to verify that increasing the session time from 2 (as per the methods of Stefanski et al., 1999) to 6 hours altered responding in a