Available online at www.sciencedirect.com
ScienceDirect
Neuroscience and Biobehavioral Reviews 32 (2008) 707–759
NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS
www.elsevier.com/locate/neubiorev

Review

Behavioral genetic contributions to the study of addiction-related amphetamine effects

Tamara J. Phillips[a,b,c,*,1], Helen M. Kamens[b,c,1,2], Jeanna M. Wheeler[b,c,3]

[a]*Veterans Affairs Medical Center, Portland, OR 97239, USA*
[b]*Methamphetamine Abuse Research Center, Oregon Health & Science University, Portland, OR 97239, USA*
[c]*Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, OR 97239, USA*

Received 14 July 2007; received in revised form 28 September 2007; accepted 28 October 2007

Abstract

Amphetamines, including methamphetamine, pose a significant cost to society due to significant numbers of amphetamine-abusing individuals who suffer major health-related consequences. In addition, methamphetamine use is associated with heightened rates of violent and property-related crimes. The current paper reviews the existing literature addressing genetic differences in mice that impact behavioral responses thought to be relevant to the abuse of amphetamine and amphetamine-like drugs. Summarized are studies that used inbred strains, selected lines, single-gene knockouts and transgenics, and quantitative trait locus (QTL) mapping populations. Acute sensitivity, neuroadaptive responses, rewarding and conditioned effects are among those reviewed. Some gene mapping work has been accomplished, and although no amphetamine-related complex trait genes have been definitively identified, translational work leading from results in the mouse to studies performed in humans is beginning to emerge. The majority of genetic investigations have utilized single-gene knockout mice and have concentrated on dopamine- and glutamate-related genes. Genes that code for cell support and signaling molecules are also well-represented. There is a large behavioral genetic literature on responsiveness to amphetamines, but a considerably smaller literature focused on genes that influence the development and acceleration of amphetamine use, withdrawal, relapse, and behavioral toxicity. Also missing are genetic investigations into the effects of amphetamines on social behaviors. This information might help to identify at-risk individuals and in the future to develop treatments that take advantage of individualized genetic information.

Keywords: Amphetamine; Methamphetamine; MDMA; Methylphenidate; Genetics; Mice; Inbred strains; Selected lines; QTL mapping; Dopamine; Glutamate

Contents

*Corresponding author at: VA Medical Center, R&D-32, 3710 SW US Veterans Hospital Road, Portland, OR 97239, USA. Tel.: +1 503 220 8262x56674; fax: +1 503 721 1029.
E-mail address: phillipt@ohsu.edu (T.J. Phillips).
[1]These authors contributed equally to this review.
[2]Now at: Yale University, 34 Park Street, 3rd Floor Research, New Haven, CT 06520, USA.
[3]Also at: VA Medical Center, R&D-32, 3710 SW US Veterans Hospital Road, Portland, OR 97239, USA.

0149-7634/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2007.10.008

1. Introduction

Illicit use of methamphetamine and methamphetamine-like drugs such as methylenedioxymethamphetamine (MDMA; "ecstasy") has increased alarmingly in the past decade. Amphetamine was once therapeutically prescribed for the treatment of depression, asthma (due to its bronchial passage dilation properties), fatigue, and weight problems, among other conditions (Anglin et al., 2000). However, its abuse potential is now well-established. The amphetamine derivative, methamphetamine, is the most commonly abused of the amphetamine-like drugs. It is easily manufactured and can be taken via several routes, including by injection, orally, by nasal inhalation, and even by smoking. Although methamphetamine has some positive effects (e.g., increased alertness), they are far outweighed by the negative consequences of chronic use. These can include paranoia, memory loss (likely due to neural toxicity in more severe cases), malnutrition, and insomnia, as well as more serious medical complications like hypertension, neural damage, death from cardiac arrhythmia, and hemorrhagic stroke.

The mechanisms of action of the amphetamine-like drugs, including amphetamine, methamphetamine, methylphenidate, and MDMA have been reviewed in detail elsewhere (Green et al., 2003; Rothman and Baumann, 2003; Sulzer et al., 2005). Amphetamines are substrates for the dopamine, norepinephrine, and serotonin transporters. Through actions at these transporters, amphetamines cause an increase in synaptic levels of the associated neurotransmitter and therefore act as indirect agonists. For example, as a substrate for the dopamine transporter (DAT), amphetamine is transported into the cytosol and disrupts the pH gradient of the synaptic vesicles, which inhibits vesicular dopamine accumulation (Sulzer and Rayport, 1990; Sulzer et al., 1995). An accumulation of cytoplasmic dopamine then allows for its release from the cell by reverse transport via the DAT (Kahlig et al., 2005). The differences among the amphetamines arise from their relative potencies at the different transporters. Amphetamine, methamphetamine, and methylphenidate have similar actions; they are more potent at inhibiting the dopamine and norepinephrine transporters compared to the serotonin transporter (Eshleman et al., 1999; Han and Gu, 2006; Rothman and Baumann, 2003; Rothman et al., 2001). However, amphetamine and methamphetamine are more potent at inhibiting norepinephrine release than dopamine release. MDMA is different from the other amphetamines in that it is most potent at inhibiting the serotonin transporter (Han and Gu, 2006), but has higher potency for inhibiting norepinephrine release than for inhibiting dopamine release (Rothman et al., 2001).

Mice are being used to define mechanisms of action of the amphetamines that are related to their abuse and toxicity (e.g., Itzhak and Ali, 2002). Genetic mouse models are being used to identify genes that may predict risk for the development of drug abuse and addiction. In particular, genetic mouse models have been used for estimating genetic correlations between drug-related traits (Crabbe, 1999), for studying the roles of specific genes in drug-relevant behavioral and biological traits (Crabbe et al., 2006; Cunningham and Phillips, 2003; Hall et al., 2004; Kieffer and Gaveriaux-Ruff, 2002; Laakso et al., 2002), and for addiction-related gene mapping (Crabbe et al., 1999; Ferraro et al., 2005; Gill and Boyle, 2003; Janowsky et al., 2001; Palmer et al., 2005). The gene mapping work has the ultimate goal of gene identification and provision of genetic information relevant to complex human diseases, such as addiction (Phillips et al., 2002a).

This review covers the behavioral genetic literature examining amphetamine-like drug traits. The genetic