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Review

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

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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

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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

models being used in amphetamine research are described as the existing data are reviewed. We have chosen not to include the cocaine-related literature in this review, but do mention specific cocaine-related studies for comparison to amphetamine effects. The information is organized by behavioral trait, starting with traits relevant to acute drug actions and progressing to more chronic drug effects, and then specific genetic information is discussed. We have not been completely inclusive, but have covered a large spectrum of the data, addressing the current state of the field with regard to genetic influences on the behavioral and physiological responses to amphetamine and amphetamine-like drugs. We note that there is a large behavioral genetic literature on responsiveness to amphetamines, but considerably less focused on genes that influence the development and acceleration of amphetamine use, withdrawal, relapse, and toxicity. In fact, the genetic influences on these different aspects of addiction liability and dependence are likely to be both unique and overlapping to some degree. Although the study of acute sensitivity traits will likely provide some insight into factors that influence the initiation of drug use, it would be beneficial to the field if more studies were aimed at defining genetic influences on traits thought to be more closely tied to the initial and plastic motivational responses to amphetamine-like drugs, excessive use of these drugs, and risk for drug dependence and relapse. For example, relatively few genetic studies have been aimed at amphetamine self-administration, using models that gauge the amount of effort an animal is willing to exert to obtain the drug, or place conditioning, which might provide information about genetic differences in sensitivity to drug–cue associations. Selective breeding procedures could be used to create lines that differ in rate or amount of amphetamine self-administered, followed by combined quantitative trait locus (QTL) and gene expression mapping to identify important genes (e.g., Palmer et al., 2005). More effort could be directed toward identifying mutants from *N*-ethyl-*N*-nitrosourea (ENU)-induced mutagenesis panels or transgenics that exhibit excessive intake or heightened risk for relapse. Existing reinstatement models and other developing models of drug relapse could be submitted to genetic analysis. Finally, genetic investigation into other important factors such as amphetamine-like drug influences on social behaviors that can be modeled in animals (e.g., Maldonado and Navarro, 2001), as well as prenatal developmental effects of amphetamines should be considered. All of this information might help to identify individuals at risk for both the development of amphetamine addiction and relapse, and could in the future lead to the development of treatments that take advantage of individualized genetic information.

2. Acute locomotor stimulation

One of the most widely investigated effects of amphetamines has been acute stimulation of locomotor behaviors. It has been suggested that acute drug stimulant effects in mice may model the euphoria experienced by humans, and may therefore be relevant at least to early drug use. It is difficult to determine the veracity of this claim. However, there are important functional connections between components of the motor system and the limbic system (brain areas shown to modulate the experience or prediction of reward), and motor behavior is required for the attainment of most rewards (Mogenson et al., 1980). The focus on acute stimulant effects may be better supported by the idea that initial drug sensitivity influences continued drug use and thus, susceptibility to the development of drug abuse and addiction. This relationship has been strongly supported for alcohol (Heath et al., 2001; Holdstock et al., 2000; Newlin and Thomson, 1999; Poikolainen, 2000; Schuckit and Smith 2000, 2001; King et al., 2002), and there are some intriguing results for psychostimulants as well. For example, the initial stimulant response to amphetamine predicted the likelihood of further drug use (de Wit et al., 1986; Gabbay, 2003), and for cocaine, there was a significant positive relationship between subjects' ratings of positive cocaine effects, including euphoria, and lifetime cocaine use (Davidson et al., 1993). However, whether these effects reflected genetically determined differences in sensitivity that is predictive of future problem drug use is not known. Studies in humans that either validate or refute a genetic relationship between sensitivity to amphetamine-induced stimulation (or another sensitivity trait) and risk for amphetamine addiction would be a benefit to those trying to model relevant phenotypes in animals.

2.1. Inbred strains

The advantages and disadvantages of inbred strain use in genetic research have been described (Crabbe, 1999; Crabbe et al., 1990; Wimer, 1992). One significant limitation is that differences in nuclear DNA may not be the source of inbred strain differences in phenotype, thus, careful interpretation is needed. Among the advantages are genetic homogeneity among the individuals of a given strain and genetic stability over time, so that data can be compared across laboratories for the same strains. Several studies have compared inbred mouse strains for their locomotor sensitivity to amphetamine-like drugs (Anisman et al., 1975; Gould et al., 2001; Hamburger-Bar et al., 1986; Kitahama and Valatx, 1979; Moisset, 1977; Moisset and Welch, 1973; Orsini et al., 2004; Ralph et al., 2001; Remington and Anisman, 1976; Wenger, 1989; Zocchi et al., 1998). Some studies report large strain differences, which, under controlled environmental conditions, could be due to genetic differences. Rat strains have also been found to be differentially sensitive to amphetamines (Camp et al., 1994; Miserendino et al., 2003; Segal et al., 1975), and one study found that the strain distribution patterns for sensitivity to the locomotor stimulant effects of cocaine and d-amphetamine were not identical (George et al.,

1991). However, even for two of the most commonly used inbred mouse strains (or sometimes their sublines), C57BL/6 and DBA/2, the strain sensitivity order for amphetamine locomotor response has not been consistent (Anisman et al., 1975; Cabib et al., 2000; Orsini et al., 2004; Phillips et al., 1994; Remington and Anisman, 1976; Wenger, 1989; Zocchi et al., 1998). Of course, it is likely that differences in the test details and other environmental circumstances have played a role in these apparent inconsistencies.

There are some strain comparisons that have attempted to relate amphetamine (or methamphetamine) sensitivity differences to neurophysiological or neurochemical differences (e.g., Camp et al., 1994). For example, Zocchi et al. (1998) found that C57BL/6 mice showed a greater, dose-dependent locomotor stimulant response to an acute injection of d-amphetamine than DBA/2 mice, which corresponded with larger increases in dopamine levels in the nucleus accumbens after d-amphetamine treatment. Although these results provide fodder for further investigation, such studies lack the power to test the hypothesis that two variables share a genetic relationship (this is discussed in greater detail below) and would require follow-up with a suitable genetic model such as a larger panel of inbred strains. Study of the putative relationship identified by Zocchi et al. (1998) in a larger strain panel might indicate whether increased nucleus accumbens dopamine is necessary for increased amphetamine stimulation.

Although recombinant inbred (RI) strains are now more commonly used for gene mapping purposes (see below), they are also useful for identifying genetic correlations and have been used to characterize genetic architecture for at least one amphetamine-related trait, namely locomotor response (Oliverio et al., 1973). Not surprisingly, the authors concluded that this trait is influenced by multiple genes. One investigation used a panel of RI strains to identify genetic correlations (common genetic influence) for the effects of methamphetamine on locomotor activity, body temperature, stereotyped chewing, and stereotyped climbing behavior. Twenty-five RI strains derived from C57BL/6J and DBA/2J inbred strain progenitors (BXD RI) were included. The strongest association was for degree of locomotor stimulation and degree of hyperthermia induced by methamphetamine (Grisel et al., 1997). It is possible that certain genes (and neurochemical mechanisms) influence both responses to methamphetamine, and also possible that high levels of locomotor behavior lead to increased body temperature. Another study used 26 of the BXD RI strains and found no evidence for a genetic correlation between the locomotor stimulant responses to phencyclidine and methamphetamine (Alexander et al., 1996). Therefore, although both drugs can produce psychotic states in humans, and they share the involvement of dopamine in their behavioral effects (Del Arco et al., 2007; Seeman et al., 2005; Zhang et al., 2001), the genetic mechanisms that determine sensitivity to these drugs may be disparate. Janowsky et al. (2001) made use of a large database of BXD RI strain means for multiple drug-related traits to identify genetic correlations with DAT density. They found that DAT density in the neostriatum was negatively genetically correlated with the acute locomotor stimulant responses to methamphetamine and cocaine, but not ethanol. Data for large strain panels tested for the motivational effects of amphetamines that might permit a direct evaluation of the genetic relationship between acute sensitivity and drug reinforcement have not been published.

2.2. Selected lines

Selective breeding results in changes in the frequencies of alleles that influence the trait of interest (see Falconer and Mackay, 1996). In theory, those that influence the trait will become fixed in the homozygous state that maximizes the trait, whereas those with no role in the trait will remain genetically segregating (if there was more than one allele in the population to begin with). The use of selected lines for studying the genetic and neurochemical underpinnings of the selected trait is intuitive. However, they are also often used to identify traits that share common genetic influence with the selection trait (i.e., genetically correlated traits). Although this may seem akin to testing two inbred strains, it is quite different because trait-relevant allele frequencies have been specifically manipulated by breeding, whereas gene frequency differences between a pair of inbred strains were not intentionally manipulated for a single trait. Thus, there is a higher probability that correlated trait differences in selected lines have, as their source, genetic differences associated with the original selection trait. This conclusion can be strengthened when similar findings are obtained in replicated selected lines (i.e., when two or more lines are selectively bred for the same trait from independent breeding populations; see Crabbe et al., 1990).

The HMACT and LMACT lines were bred for high and low methamphetamine activation responses, respectively, after a 2 mg/kg dose of methamphetamine (Kamens et al., 2005). The lines exhibited a 5-fold difference in methamphetamine activation response in the last generation of selection (generation 4). They were also found to differ in acute locomotor response to cocaine and ethanol (HMACT > LMACT in both cases), and the LMACT line consumed more methamphetamine, cocaine, and ethanol than the HMACT line in two-bottle choice tests versus water (Kamens et al., 2005, 2006). Thus, heightened sensitivity to the acute stimulant effects of methamphetamine appears to confer protection against high levels of methamphetamine, cocaine, and ethanol self-administration. This result is contrary to that predicted from the human literature on alcohol that has suggested that greater sensitivity to the behavioral stimulant effects of alcohol is associated with a positive family history of alcoholism (Newlin and Thomson, 1999) and with heightened levels of alcohol consumption (Holdstock et al., 2000; King et al., 2002). However, it is possible that with methamphetamine, there is a biphasic relationship such that modest levels of

stimulation are pleasant and extreme levels aversive. Examination of methamphetamine in the selected lines at various stages of the selection might have revealed a positive genetic association between stimulation and drinking at a stage of less-extreme stimulation.

The method used for the creation of these lines was mass selection (i.e., breeding the highest scoring animals to each other and the lowest scoring animals to each other, regardless of their relatedness except that sib mating is excluded). This selection method results in a rapid response, but with the cost of an increased rate of inbreeding, compared to some other methods (and thus, an increased probability of the chance fixation of selection trait-irrelevant alleles). However, when the number of selection generations is kept small (i.e., $\leqslant 5$), excessive inbreeding can be avoided (Belknap et al., 1997). Since only one set of HMACT and LMACT lines was created, it is reasonable to question whether the correlated trait differences were associated with selection trait-relevant genes or with those differing in frequency between the lines due to random drift (inbreeding). Data from other sets of selected lines help to address this question.

The FAST and SLOW selected lines were bred in replicate for 37 generations (i.e., there is a FAST-1 and FAST-2 line and a SLOW-1 and SLOW-2 line) for increased and decreased sensitivity to the locomotor stimulant effects of ethanol, respectively (Crabbe et al., 1987; Phillips et al., 1991, 2002b; Shen et al., 1995). A within-family rotational breeding scheme was used for this long-term selection project to reduce inbreeding. In earlier selection generations, there was little evidence for a genetic correlation between locomotor sensitivity to d-amphetamine and ethanol (Phillips et al., 1992). Later in selection, a difference in response to methamphetamine arose in one replicate set of the FAST and SLOW lines (Bergstrom et al., 2003). We do not believe that these results are peculiar to methamphetamine, as the same pattern of results was found for d-amphetamine (Phillips, unpublished data). In an even later generation, a significant line difference in one replicate and a statistical trend toward a line difference in the other was found for methamphetamine response (Bergstrom et al., 2003). These results provide strong evidence for some common genetic regulation of the locomotor stimulant responses to ethanol and methamphetamine. There has also been a study in humans showing that subjects who experienced more pronounced stimulant-like effects from ethanol reported greater stimulant effects from amphetamine (Holdstock and de Wit, 2001). However, the study design did not allow for determination of whether the relationship was due to common genetic influences or not.

The late appearance of the differences in response to methamphetamine between FAST and SLOW mice, compared to the early divergence of the lines in response to ethanol, suggests that genes recruited later in the selection, and thus with a more minor impact on ethanol sensitivity are those which also influence the locomotor stimulant response to methamphetamine. This conclusion is consistent with the small magnitude of difference in stimulant response to ethanol found between the HMACT and LMACT selected lines (Kamens et al., 2006). Similar results with respect to both line and replicate were found when FAST and SLOW mice were tested for stimulant response to cocaine (Bergstrom et al., 2003; Phillips and Shen, 1996). Further, two lines of mice bred for their large locomotor stimulant response to cocaine exhibited a larger stimulant response to d-amphetamine, compared to two lines bred for low cocaine response (Marley et al., 1998). Finally, Short Sleep mice bred for decreased sensitivity to the sedative–hypnotic effects of ethanol have been found to exhibit heightened sensitivity to the locomotor stimulant effects of (+)amphetamine, cocaine, and ethanol, compared to Long Sleep mice, which were bred for increased sensitivity to the sedative–hypnotic effects of ethanol (Hanania and Zahniser, 2002).

Collectively, the results from multiple sets of selected lines suggest some shared genetic regulation of sensitivity to the locomotor stimulant effects of amphetamine, ethanol and cocaine. This is not surprising considering the evidence that all three drugs, given in doses that stimulate locomotion, increase dopamine signaling. However, as mentioned above, DAT density in the neostriatum appears to be a shared mechanism determining sensitivity to the locomotor stimulant effects of methamphetamine and cocaine, but not of ethanol.

3. Stereotypy

High-dose amphetamine treatment or repeated treatment can result in repetitive movements commonly referred to as stereotypy. In rodents, stereotypic behaviors may include head swaying or bobbing, repetitive forelimb movements, repetitive chewing, and self-mutilation (Atkins et al., 2001; Grisel et al., 1997; Mueller et al., 1982). In humans, methamphetamine-induced stereotypic behavior is sometimes referred to as "punding". Punding may be defined as compulsively performing a useless task over and over again (Schiorring, 1981). Examples are repetitively assembling and disassembling a multicomponent item, or repetitive stacking and unstacking of magazines. In addition to stereotypy, with excessive amphetamine use, schizophrenia-like symptoms may develop that are often indistinguishable from non-drug-induced schizophrenia. Dopaminergic alterations thought to underlie stereotypic behaviors also appear to be responsible for these schizophrenia-like symptoms. Certain psychological aspects of amphetamine-induced schizophrenia-like symptoms, such as delusions, cannot be modeled in animals; however, there have been a few investigations of genetic influences on amphetamine-induced stereotypy.

3.1. Inbred strains

Recently, a set of inbred strains has been characterized for vertical leaping behavior (sometimes called "popping,"

"jumping," or "hopping") induced by high-dose d-amphetamine (10 mg/kg; McKerchar et al., 2006). The authors suggest that pharmacologically induced leaping behavior may be a relevant model for studying schizophrenia. Whether or not to include vertical leaping among the stereotypic behaviors is not clear, but it does not appear to occur at lower acute doses of amphetamines (Colpaert et al., 1975; Lal et al., 1975, 1976). Among the five inbred strains and one outbred stock examined, only the BALB/cJ strain exhibited vertical leaping behavior in response to d-amphetamine (McKerchar et al., 2006). McKerchar et al. (2006) describe some similarities in strain sensitivities to vertical leaping induced by d-amphetamine, dizocilpine (Deutsch et al., 1997), and naloxone-precipitated morphine withdrawal (Kest et al., 2002), although they point out the difficulty in making meaningful comparisons due to differences in dosing regimens and methods for quantification. In the course of measuring leaping behavior across the 5 treatment days, behavioral sensitization was seen in bouts of low mobility (a measure of spatial confinement due to focused stereotypy). However, the pattern of increase across treatment days did not differ significantly among the genotypes (McKerchar et al., 2006). Thus, genetic differences among these mouse genotypes did not influence magnitude of sensitization to the stereotypic effects of the drug.

3.2. Selected lines

The HMA and LMA lines were bred for high and low numbers of stereotyped chewing episodes, respectively, in response to 10 mg/kg methamphetamine (Atkins et al., 2001). The dose of methamphetamine used for selection was adjusted after the second selection generation to avoid floor and ceiling effects. These lines were bred using mass selection for a total of four selection generations. At the end of selection, when tested for response to the original 10 mg/kg dose of methamphetamine, the lines exhibited a 7-fold difference in number of stereotyped chewing episodes. Locomotor stimulant responses to methamphetamine (measured as line crossings in the home cage) at doses up to 3.5 mg/kg were identical for the two lines. At doses of 7 mg/kg and higher, LMA mice exhibited more locomotor behavior, perhaps because the HMA line was experiencing more competing stereotypy behaviors at these doses. In fact, the LMA mice also exhibited higher stereotyped circling and climbing behaviors after methamphetamine treatment, compared to HMA mice. The fact that sensitivity to more purely stimulating doses of methamphetamine was similar in these lines indicates that methamphetamine-induced activation and stereotypy do not share common genetic regulation. This is an important point in the formulation of hypotheses about the development of problem amphetamine use versus the maintenance of excessive amphetamine use. Genetic factors that influence each of the stages in a psychostimulant abuse syndrome may be non-, or only partially, overlapping.

4. Locomotor sensitization

When administered repeatedly at daily or less-frequent intervals, there is enhanced sensitivity to the motoric and stereotypic effects of amphetamines, a phenomenon referred to as behavioral sensitization. Many opinions have been expressed regarding the importance of sensitization to addiction. Bartlett et al. (1997) have hypothesized that the neuroadaptations underlying behavioral sensitization contribute to the paranoia and psychosis characteristic of psychostimulant abuse. Robinson and Berridge (1993) have proposed that repeated drug use renders certain neural systems sensitized to drugs and drug-associated stimuli, leading to a pathological focus on drug-associated stimuli, which then come to exert powerful control over behavior (such as drug-seeking behavior). Koob and Le Moal (2006) have expressed the opinion that sensitization is not worthy of consideration in models of drug dependence. However, they do concede a possible role of sensitization in the early phase of drug use, perhaps because sensitization can be seen after a single previous drug exposure (Robinson et al., 1982; Vanderschuren et al., 1999). Further, a role in relapse seems plausible given that psychostimulant sensitization is extremely long-lasting and is best seen with intermittent schedules of drug administration (Kuribara, 1996; Robinson, 1984). Animal models that measure behavioral sensitization provide behavioral markers of neuroadaptation induced by repeated drug exposure. Although there have been many studies exploring the neurobiological mechanisms associated with psychostimulant sensitization, few studies have focused on genetic differences that may influence susceptibility to behavioral sensitization, nor has the field found a convincing way to demonstrate a causal relationship between sensitization seen behaviorally or neurochemically and a change in motivational response to a psychostimulant drug. Further, it is likely that the genetic influences on context-dependent (conditioned) and context-independent (pharmacological) sensitization are not entirely the same, and that each type may play a different role in the development of addiction and in relapse to drug use, following periods of abstention. These speculative comments can be validated (or refuted) only by direct investigation.

4.1. Inbred strains

Few studies have been performed examining strain differences in behavioral sensitization to amphetamines. Comparing C57BL/6J and DBA/2J strain mice, DBA/2J mice were more sensitive to the development of sensitization to methamphetamine when the sensitizing agent was either repeatedly administered methamphetamine (Phillips et al., 1994) or repeated daily restraint stress (Badiani et al., 1992). However, the opposite strain order has also been reported for repeated amphetamine-induced sensitization (Cabib, 1993).

4.2. Selected lines

To our knowledge, selection for magnitude of sensitization has not been attempted for any drug. However, degree of sensitization to methamphetamine was assessed during each generation of selection for acute methamphetamine sensitivity in the HMACT and LMACT lines. No differences in magnitude of sensitization were found when the treatment and test dose was 2 mg/kg. However, when sensitization was examined in response to a lower dose of methamphetamine (1 mg/kg), the HMACT line exhibited more behavioral sensitization than the LMACT line (Kamens et al., 2005). The authors speculated that the line difference was not observable at the higher dose of methamphetamine due to a ceiling effect. The lines were also examined for sensitization to a 10 mg/kg dose of cocaine, and did not differ. Unfortunately, no other doses of cocaine were used, and the lines are extinct. We are currently selectively breeding mice for high and low sensitization to methamphetamine and will be testing these lines for correlated psychostimulant-related and possibly ethanol-related traits during the course of selection.

5. Reward and conditioned effects

Surprisingly, few studies have examined genetic contributions to the rewarding effects of amphetamines using measures like self-administration or conditioned place preference. We believe that greater attention needs to be aimed in this direction. However, it is necessary to acknowledge that most mammalian genetic studies utilize mice because of the wealth of genetic information available for this species, and that data using the preferred route of psychostimulant self-administration, intravenous, is technically difficult to obtain in mice, although not impossible (Yan et al., 2006). We have utilized an oral route of self-administration in our genetic studies (Kamens et al., 2005), but we assume that there will be healthy skepticism regarding the veracity of the claim that this reflects differential reinforcement until we can demonstrate concordance of our results with more widely accepted measures, such as intravenous self-administration or conditioned place preference.

Although place conditioning procedures appear to offer a less technically challenging method for the measurement of the rewarding effects of drugs, it can be difficult to demonstrate place preference, rather than place aversion, to amphetamine-like drugs in mice. This method offers a different dimension to the study of drug reinforcement, compared to self-administration, in that it focuses on the important role of cues that have been assigned biological significance by virtue of their association with reinforcing drug effects. Comparisons of C57BL/6J and DBA/2J mice suggest that the former strain develops a preference for locations formerly associated with amphetamine and the latter strain develops an aversion, but that these outcomes can be influenced by environmental factors (Cabib et al., 2000; Orsini et al., 2004). Conditioned taste aversion methods offer another means for examining the motivational effects of drugs. Taste aversion induced by amphetamine treatment was similar for C57BL/6J and DBA/2J mice (Orsini et al., 2004), but has not been used in models appropriate for genetic analysis.

Some studies suggest that response to novelty can predict faster acquisition of amphetamine self-administration (Piazza et al., 1989, 1990). However, in those studies, rats were separated into subgroups based on locomotor response in a novel environment. This design does not permit attribution of the locomotor differences to genetic differences. In an attempt to develop a genetic animal model that could be used to examine the notion that novelty-related behavior might be genetically associated with sensitivity to drug reward, Kliethermes et al. (2007) report the selective breeding of mice for divergent exploration of a hole-board apparatus. When tested for differential sensitivity to d-amphetamine-induced place conditioning, no consistent line differences were found. Further, the lines did not differ in level of methamphetamine self-administration or in behavioral sensitization to methamphetamine. These results do not support a genetic relationship between novelty seeking reflected in the head dipping behavior and drug reward. However, as noted by the authors, if their selection trait had been based on a measure of explicit novelty seeking, the genetic correlation results may have been different.

6. Neurotoxicity

Brain alterations associated with chronic methamphetamine abuse have been documented in humans using imaging techniques (McCann et al., 1998; Volkow et al., 2001; Wang et al., 2004). Neurotoxic effects on striatal dopamine systems are well-established from animal research (Davidson et al., 2001; Schmidt et al., 1985), although the role of hyperthermia versus more direct drug effects is not entirely clear (Yuan et al., 2006). It has been suggested that reactive oxygen species play a critical role in the toxic effects of chronic methamphetamine use through methamphetamine-induced hyperthermia, changes in dopamine or glutamate transmission, and mitochondrial disruption (Riddle et al., 2006). Some components of dopamine systems appear to recover from chronic methamphetamine effects, whereas others do not (Segal et al., 2005). Although the behavioral consequences of treatment with neurotoxic doses of methamphetamine have received some attention (e.g., Itzhak and Ali, 2002), the research in this area is not extensive and has not focused on the question of genetic influences on susceptibility to neurotoxic effects. This is an area of importance because it may explain some of the variation among individuals in the magnitude of negative impact of excessive amphetamine use. There are several studies using single-gene mutant mice to examine the neurotoxic effects of amphetamine-like drugs (e.g., Fumagalli et al., 1998, 1999; Itzhak et al., 2004;

Perez et al., 2005; Numachi et al., 2007), but few have examined behavior, and thus this literature will not be discussed here.

7. Genetic findings from mapping and mutants

7.1. Gene mapping

The use of QTL mapping for addiction-related traits in mice began about 15 years ago (Gora-Maslak et al., 1991). For a primer on QTL theory and methods in different genotype structures, see Palmer and Phillips (2000). A quantitative trait, sometimes referred to as a complex trait, is one influenced by multiple genetic and environmental factors. Initial QTL mapping identifies chromosomal regions that harbor genes that contribute to variation in the trait of interest. Finer mapping may then ensue to narrow the region to one containing a small number of genes. Examination of existing sequence information or additional sequencing may be used to identify functional polymorphisms that may account for behavioral variation. Gene expression analyses may also be used to identify genes in the region that are differentially expressed depending upon magnitude of the behavioral trait. For additional information and issues regarding the search for quantitative genes, several papers are available at every level of complexity (e.g., Belknap et al., 2001; Nadeau and Frankel, 2000; Phillips et al., 2002a; Willis-Owen and Flint, 2007; Wu and Lin, 2006). Table 1 summarizes the existing QTL mapping data for amphetamine-related behavioral and thermal traits. The data are sparse, and many of the QTL are considered provisional. In other words, they are supported at a statistical level that will require additional confirmatory evidence. Some of the QTL are considered to be definitive, but the specific genes that are responsible for determining trait variation have not yet been identified.

7.2. Recombinant inbred (RI) strains

The use of RI strains to identify traits that share common genetic influence (genetic correlation) was described above. In the past two decades, RI strains have also been used to identify trait-specific QTL, including QTL for amphetamine-related traits. As nicely reviewed by Belknap and Crabbe (1992), RI strains were originally developed for major gene mapping. However, technological advances

Table 1
Quantitative trait loci (QTL) mapped in mice for behavioral and thermal responses to amphetamine and methamphetamine

Chr	Locomotor activity	Hyperthermia	Stereotypy
1	4 mg/kg MA in BXD RI[a] 5 mg/kg AMP A.B/B.A RCS[b] 16 mg/kg MA in BXD RI[a]	4 mg/kg MA in BXD RI[a] 8 mg/kg MA in BXD RI[a] 16 mg/kg MA in BXD RI[a] 20 mg/kg AMP in BXD RI[c,d]	16 mg/kg MA climbing in BXD RI[a]
2	5 mg/kg AMP AXB/BXA RCS[b]		8 mg/kg MA chewing in BXD RI[a] 16 mg/kg MA climbing in BXD RI[a]
3	4 mg/kg MA in BXD RI[a] 5 mg/kg AMP A.B/B.A RCS[b] 8 mg/kg MA in BXD RI[a]	4 mg/kg MA in BXD RI[a] 16 mg/kg MA in BXD RI[a] 20 mg/kg AMP in BXD RI[d]	
4	5 mg/kg AMP in BXD RI[e]	16 mg/kg MA in BXD RI[a]	8 mg/kg MA chewing in BXD RI[a] 16 mg/kg MA climbing in BXD RI[a]
5	2 mg/kg MA STSL[f] 5 mg/kg AMP in BXD RI[e] 5 mg/kg AMP A.B/B.A RCS[b] 8 mg/kg MA in BXD RI[a]		8 mg/kg MA chewing in BXD RI[a] 16 mg/kg MA climbing in BXD RI[a]
6	4 mg/kg MA in BXD RI[a] 5 mg/kg AMP in BXD RI[e] 5 mg/kg AMP A.B/B.A RCS[b] 8 mg/kg MA in BXD RI[a]	4 mg/kg MA in BXD RI[a] 8 mg/kg MA in BXD RI[a] 16 mg/kg MA in BXD RI[a] 20 mg/kg AMP in BXD RI[d]	
7	4 mg/kg MA in BXD RI[a] 8 mg/kg MA in BXD RI[a]	4 mg/kg MA in BXD RI[a] 8 mg/kg MA in BXD RI[a] 16 mg/kg MA in BXD RI[a]	
8	4 mg/kg MA in BXD RI[a] 5 mg/kg AMP in BXD RI[e] 5 mg/kg AMP A.B/B.A RCS[b]	16 mg/kg MA in BXD RI[a]	16 mg/kg MA climbing in BXD RI[a]
9	2 mg/kg MA STSL[f] 5 mg/kg AMP A.B/B.A RCS[b] 8 mg/kg MA in BXD RI[a] 16 mg/kg MA in BXD RI[a]	4 mg/kg MA in BXD RI[a] 8 mg/kg MA in BXD RI[a] 16 mg/kg MA in BXD RI[a]	8 mg/kg MA chewing in BXD RI[a]

Table 1 (*continued*)

Chr	Locomotor activity	Hyperthermia	Stereotypy
10	5 mg/kg AMP A.B/B.A RCS[b] 16 mg/kg MA in BXD RI[a]	4 mg/kg MA in BXD RI[a]	
11	2 mg/kg MA STSL[f]		
12	2 mg/kg MA STSL[f] 4 mg/kg MA in BXD RI[a]	4 mg/kg MA in BXD RI[a] 8 mg/kg MA in BXD RI[a] 16 mg/kg MA in BXD RI[a]	
14	5 mg/kg AMP in BXD RI[e] 8 mg/kg MA in BXD RI[a] 16 mg/kg MA in BXD RI[a]	16 mg/kg MA in BXD RI[a]	16 mg/kg MA climbing in BXD RI[a]
15	2 mg/kg MA STSL[f] 8 mg/kg MA in BXD RI[a] 16 mg/kg MA in BXD RI[a]		
16	8 mg/kg MA in BXD RI[a]	16 mg/kg MA in BXD RI[a]	
17	5 mg/kg AMP A.B/B.A RCS[b] 16 mg/kg MA in BXD RI[a]	16 mg/kg MA in BXD RI[a] 20 mg/kg AMP in BXD RI[d]	8 mg/kg MA chewing in BXD RI[a] 16 mg/kg MA climbing in BXD RI[a]
18	5 mg/kg AMP in BXD RI[e]		
19		4 mg/kg MA in BXD RI[a] 8 mg/kg MA in BXD RI[a] 16 mg/kg MA in BXD RI[a]	
X	5 mg/kg AMP A.B/B.A RCS[b]		8 mg/kg MA chewing in BXD RI[a]

Listed are the chromosomes harboring QTL, drug and dose, and genetic mapping population. The length of the QTL support interval and strength of statistical evidence in support of the QTL varies across studies. A = A/J; AMP = amphetamine; B = C57BL/6J; Chr = chromosome; D = DBA/2J; MA = methamphetamine; RCS = recombinant congenic strain; RI = recombinant inbred strain; STSL = short-term selected lines.

[a]Grisel et al. (1997).
[b]Torkamanzehi et al. (2006).
[c]Belknap and Crabbe (1992).
[d]Gora-Maslak et al. (1991).
[e]Alexander et al. (1996).
[f]Palmer et al. (2005).

have resulted in their use for the mapping of minor gene loci—regions harboring genes relevant to multigenically mediated traits. Some of the earliest mapping data for an amphetamine-related trait assessed in mice were obtained using hyperthermia data collected by Seale et al. (1985) for 10 of the BXD RI. These data were subjected to QTL mapping first by Gora-Maslak et al. (1991) and then again using a denser marker set (Belknap and Crabbe, 1992). The most significant result for a gene influencing the hyperthermic response to a single dose of 20 mg/kg d-amphetamine was for a locus on mouse chromosome 1. We are not aware of any attempts to directly identify the influential gene responsible for what appeared to be a major single-gene effect. However, in a more recent study (Grisel et al., 1997), BXD RI mice were used for mapping the hyperthermic response to three doses of methamphetamine (4, 8 and 16 mg/kg). A region of interest was identified on chromosome 1; however, a major gene effect was not strongly indicated in this 27-strain study, as it was in the previous 10-strain study. One possible explanation for non-confirmation of a major gene effect is that the QTL is dose-specific. Another is that the original finding was a false positive. Finer mapping would be needed to examine the possibility that one or more genes influence this response in this region of chromosome 1. Associations with genes on other chromosomes were also indicated.

Other amphetamine-related traits that have been subjected to gene mapping efforts using RI strains include methamphetamine-induced stereotyped climbing, repetitive chewing, and acute locomotor activation (Grisel et al., 1997; Torkamanzehi et al., 2006). In all cases, provisional QTL have been identified, but additional work is needed for confirmation, finer mapping, and gene identification. None of these works have yet progressed to the point where a quantitative trait gene (QTG) has been definitively identified based on collective evidence (see Belknap et al., 2001; Phillips et al., 2002a) from initial QTL mapping. Data for methamphetamine-induced place conditioning in a set of the BXD RIs were used for correlation with DAT binding (Janowsky et al., 2001); however, the gene mapping results have not been published (CL Cunningham, personal communication).

7.3. Selected lines

QTL can also be mapped using selected lines. To our knowledge, the only selected lines that have been used to map an amphetamine-related trait are the HMACT and LMACT lines, bred for high and low sensitivity to the acute stimulant effects of methamphetamine. QTL analyses using DNA from mice of these lines provided evidence that there are genes that influence sensitivity to methamphetamine on chromosomes 5, 9, 11, 12, and 15 (Palmer et al., 2005). In an attempt to align possible differences in gene expression with genes that reside within these QTL regions, nucleus accumbens tissue from the HMACT and LMACT lines was used in a microarray gene expression analysis. Because the mice were not methamphetamine-treated prior to brain biopsy, these differentially expressed genes represent innate genetic differences that might be expected to influence methamphetamine response. Of the genes found to be differentially expressed, some reside in the methamphetamine sensitivity QTL regions (Palmer et al., 2005). Casein kinase (*Csnk1e*) resides in the chromosome 15 QTL region and was differentially expressed. This is a particularly interesting candidate gene for an influence on sensitivity to methamphetamine because the Csnk1e protein is known to increase the activity of DARPP-32 (dopamine- and adenosine 3′,5′-monophosphate (cAMP)-regulated phosphoprotein of 32 kilodaltons). DARPP-32 is phosphorylated after psychostimulant administration through increasing extracellular dopamine levels, and is a likely player in the regulation of the locomotor response to psychostimulant drugs (Greengard, 2001). A difference in *Darpp-32* expression between the HMACT and LMACT lines was also found (Palmer et al., 2005). This work was translated to an investigation of healthy human volunteers in which their subjective responses to placebo, 10 or 20 mg of d-amphetamine was examined and compared to polymorphisms in the CSNK1E region. The subjects' ratings of whether they felt a drug effect was significantly associated with one single-nucleotide polymorphism in that region (Veenstra-VanderWeele et al., 2006). Thus, casein kinase 1 epsilon allelic variation is a strong candidate for predicting amphetamine responsiveness in the human and mouse.

7.4. Single-gene mutants

Tables 2–9 summarize the large number of amphetamine response studies that have been performed using mice carrying single-gene mutations. In these tables, we have included the most accurate genetic background information that we could glean from the published literature, as this may affect interpretation. In some cases, these mutations are naturally occurring, some were targeted and created using homologous recombination (knockout mice; KO), and some are over- or under-expression transgenics. Methods for creation of single-gene mutant mice by homologous recombination and some of the issues associated with the almost exclusive use of 129 strains as the source of embryonic stem (ES) cells were recently summarized in an update by Seong et al. (2004). Several additional readings on this topic are cited in that paper, and we have had personal experience with experimental results in mutant mice that appear to have been influenced by varying genetic backgrounds (Phillips et al., 1999; Phillips and Belknap, 2002). Although we have made an attempt to be comprehensive, there is some probability that papers have been omitted, and of course new papers have been published since our search was completed. Further, our interpretation of the data may differ from that of these authors; we leave it to the reader to form their own opinions. Selected information from each of the tables is discussed below, with the exception of Table 9, which summarizes information that did not fit well into the other tables. The reader interested in a similar review of research in single-gene mutants for ethanol-related traits is referred to Crabbe et al. (2006).

8. Dopamine-related genes: amphetamine and methamphetamine (Table 2)

The known actions of amphetamines and methamphetamine on dopaminergic systems have created interest in the role of dopamine-related genes in the responses to these drugs. The influence of gene knockout on several behavioral responses to these stimulant drugs has been examined. The preponderance of studies has concentrated on locomotor sensitivity and sensitization; however, reward-related and sensory gating traits, such as place conditioning, brain stimulation reward, and prepulse inhibition (PPI), have also been examined. Sensory gating deficits have been a focus due to their possible relevance to the deficits seen in psychostimulant addiction.

Both pharmacological and gene manipulation approaches have been used to study the role of the dopamine system in behavioral responses to amphetamines, but results across approaches have not always agreed. For example, cocaine- and amphetamine-regulated transcript (CART) was identified as an mRNA transcript that is upregulated in the striatum following an injection of psychostimulants (Douglass et al., 1995). Intra-ventral tegmental area administration of the CART peptide has been shown to dose-dependently increase locomotor activity and to induce conditioned place preference (Kimmel et al., 2000). However, when basal locomotor activity was examined in CART KO and wild-type (WT) mice, no difference was found. Further, the two genotypes showed equal sensitivity to the low-dose (1 and 3 mg/kg) stimulant effects of amphetamine, but at a higher dose (6 mg/kg) the WT mice were less sensitive than the KO mice (Couceyro et al., 2005); no differences in stimulant response to 1, 2, 4 or 8 mg/kg amphetamine were found in another study (Moffett et al., 2006). Conversely, WT mice showed enhanced conditioned place preference to 0.3 mg/kg amphetamine compared to CART KO mice (Couceyro et al., 2005), suggesting that the CART peptide

Table 2
Dopamine-related studies in single-gene mutants for methamphetamines and amphetamines

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Karper et al. (2002)	$D_{1A}R$ (dopamine D1 receptor)	WT, KO	129/Sv J1 ES cells, 129/Sv × C57BL/6 hybrid	M/F	d-Amphetamine sulfate	1, 2, 4, and 8 mg/kg (× 7, once per day) for development of sensitization; 1 mg/kg for expression of sensitization after 3 and 17 days abstinent	WT = KO for baseline locomotion; WT = KO for acute stimulation	WT = KO for sensitization development and expression				
Crawford et al. (1997)	$D_{1A}R$ (dopamine D1 receptor)	WT, KO	129/Sv J1 ES cells, 129/Sv × C57BL/6 hybrid, backcrossed	M/F	d-Amphetamine	2 mg/kg (× 5, once per day) for development of sensitization; 2 mg/kg for expression of sensitization after 4 days abstinent	WT = KO for baseline locomotion; WT = KO for acute stimulation (no acute stimulation in either genotype)	WT > KO for both development and expression of sensitization				
Xu et al. (2000b)	D_1R (dopamine D1 receptor)	WT, KO	129/Sv D3 ES cells, 129/Sv × C57BL/6 hybrid	M/F	d-Amphetamine sulfate	1, 2, and 5 mg/kg for acute; 5 mg/kg (× 7, once per day) for sensitization development	Acute stimulation: WT > KO (2 mg/kg) WT = KO (1 and 5 mg/kg)	KO ⩽ WT for development of sensitization (outcome complicated by differences in saline control group responses)		WT = KO for grooming frequency after acute (1, 2 and 5 mg/kg) and repeated (5 mg/kg) administration		Rearing: WT > KO (1 mg/kg), WT = KO (2 and 5 mg/kg)
McDougall et al. (2005)	D_1R (dopamine D1 receptor)	WT, KO	129/Sv J1 ES cells, 129/Sv × C57BL/6 hybrid	M/F	d-Amphetamine sulfate	8 mg/kg (× 7, once per day) for development of sensitization, 1 mg/kg expression test after 17 days abstinence; or 8 mg/kg once then tested with 1 mg/kg after 2 or 17 days abstinent	KO > WT for acute stimulation (8 mg/kg)	KO > WT for development (across 7 days) and expression of sensitization after 7 injections; KO = WT for expression of sensitization after a single pre-exposure				
Ralph-Williams et al. (2002)	D_1R (dopamine D1 receptor)	WT, HET, KO	129/Sv J1 ES cells, 129/Sv × C57BL/6 hybrid, N7 backcross to C57BL/6J	M/F	d-Amphetamine	10 mg/kg					WT = HET = KO for depressant effect of amphetamine on % PPI	
Dracheva et al. (1999)	D_1R (dopamine D1 receptor overexpression)	Non-TG, TG	C57BL/6J × DBA/2J hybrid, N2–N4 backcross to C57BL/6	NS	d-Amphetamine sulfate	2 mg/kg	Non-TG = TG for baseline locomotion; non-TG = TG for acute stimulation					
Glickstein and Schmauss (2004a)	D_2R (dopamine D2 receptor)	WT, KO	129/Sv R1 ES cells, 129/Sv × C57BL/6 hybrid	M	s-Methamphetamine	5 mg/kg once for memory test; 5 mg/kg (× 3, once every 2 h) for stereotypy				WT > KO		Spatial memory: WT > KO at baseline; WT = KO after methamphet-amine

Table 2 (*continued*)

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Chen et al. (2001)	D_2R (dopamine D2 receptor)	WT, KO	129/Sv D3 ES cells, 129/Sv × C57BL/6J hybrid, N6 backcross to C57BL/6J	NS	Amphetamine	2.5 mg/kg	WT > KO for baseline locomotion; KO > WT for locomotor stimulation when corrected for baseline difference					
Ralph et al. (1999)	D_2R (dopamine D2 receptor)	WT, HET, KO	129/Sv D3 ES cells, 129/Sv × C57BL/6J hybrid, N5 backcross to C57BL/6J 10 mg/kg	M/F	d-Amphetamine sulfate						WT = HET = KO for baseline % PPI; WT > HET > KO for depressant effect of amphetamine on % PPI	
Elmer et al. (2005)	D_2R (dopamine D2 receptor)	WT, HET, KO	129/Sv D3 ES cells, 129/Sv × C57BL/6J hybrid, N10 backcross to C57BL/6J	M	Amphetamine	1, 2, and 4 mg/kg tested in ascending order						Brain stimulation reward: WT > KO for sensitivity (HET not directly compared); WT = HET = KO for amphetamine-induced decrease in required threshold stimulation
Ralph-Williams et al. (2002)	D_2R (dopamine D2 receptor)	WT, HET, KO	129/Sv D3 ES cells, 129/Sv × C57BL/6J hybrid, N8 backcross to C57BL/6J	M/F	d-Amphetamine	10 mg/kg					WT > HET = KO for depressant effect of amphetamine on % PPI	
Xu et al. (2002)	D_2LR (dopamine D2 receptor-long isoform)	WT, KO	129/terSv J1 ES cells, 129/terSv × C57BL/6 hybrid, N6 backcross to C57BL/6	M	Amphetamine	10 mg/kg					WT = KO for baseline startle magnitude and % PPI; WT = KO for depressant effect of amphetamine on % PPI	
Fetsko et al. (2003)	D_2LR (dopamine D2 receptor –long isoform)	WT, HET, KO	129/terSv J1 ES cells, N6 backcross to C57BL/6	M	d-Amphetamine	16 mg/kg				Biting: WT = HET > KO; Climbing: WT > HET = KO; Licking: WT = HET = KO; Grooming: WT = HET = KO; Head movement: KO > HET = WT (16 mg/kg)		

Glickstein and Schmauss (2004b)	D_2R and D_3R (dopamine D2 and D3 receptors)	WT, D2KO, D3KO, double D2/D3KO	All mutants: 129/Sv R1 ES cells, 129/Sv × C57BL/6 hybrid	M	s-Methamphetamine	5 mg/kg (× 3, once every 2 h)				D2: WT > KO D3: WT = KO D2/D3: WT > KO		
Glickstein and Schmauss (2004a)	D_3R (dopamine D3 receptor)	WT, KO	129/Sv R1 ES cells, 129/Sv × C57BL/6 hybrid	M	s-Methamphetamine	5 mg/kg once for memory test; 5 mg/kg (× 3, once every 2 h) for stereotypy				WT = KO		Spatial memory: WT > KO at baseline and after methamphetamine
McNamara et al. (2006)	D_3R (dopamine D3 receptor)	WT, KO	129/Sv D3 ES cells, 129/Sv × C57BL/6 hybrid, N3 backcross to C57BL/6	M	d-Amphetamine sulfate	0.2, 2.5, 5, and 10 mg/kg	KO > WT for acute stimulation to 2.5 mg/kg; WT = KO for acute stimulation to 0.2, 5 and 10 mg/kg			WT = KO (0.2, 2.5, 5, and 10 mg/kg)		
Xu et al. (1997)	D_3R (dopamine D3 receptor)	WT, KO	129/Sv D3 ES cells, 129/Sv × C57BL/6 hybrid	M	d-Amphetamine sulfate	0.04, 0.1, 0.5, 5 mg/kg (× 2, every other day)			KO > WT during first 2 min of test and at a lower dose during the 20-min test			
Ralph et al. (1999)	D_3R (dopamine D3 receptor)	WT, KO	129/SvJ E14 ES cells, 129/SvJ × C57BL/6 hybrid	M/F	d-Amphetamine sulfate	10 mg/kg					WT = KO for baseline % PPI; WT = KO for depressant effect of amphetamine on % PPI	
Chen et al. (2007)	D_3R (dopamine D3 receptor)	WT, HET, KO	129S4/SvJae J1 ES cells, 129SvJae × C57BL/6 hybrid, N5-8 backcross to C57BL/6	M/F	Methamphetamine	2 mg/kg (× 8, once per day) for sensitization/stereotypy development, 0.5 mg/kg for expression of sensitization/stereotypy after 3 days abstinent; 2 mg/kg (× 4, every other day) for CPP	WT = HET = KO for baseline locomotion; WT = HET < KO for acute stimulation (2 mg/kg)	KO > WT = HET for rate of sensitization development; KO > WT (HET not tested) for expression of sensitization	KO > WT = HET	KO > WT for expression of stereotypy		
Rubinstein et al. (1997)	D_4R (dopamine D4 receptor)	WT, KO	129/Ola Hsd E14TG2a ES cells × C57BL/6J F2 hybrid	M/F	Methamphetamine	1 and 2 mg/kg	KO > WT for acute stimulation (1 and 2 mg/kg)					
Kruzich et al. (2004)	D_4R (dopamine D4 receptor)	WT, KO	129/SvEv ES cells × C57BL/6J, N10 backcross to C57BL/6J	M	d-Amphetamine sulfate	1, 3, and 10 mg/kg for acute; 2 mg/kg for expression of sensitization 28 days post acute dose. OR 1.5, 3, and 6 mg/kg for acute; same doses for expression of sensitization 1 week later	WT = KO for acute stimulation to 1 mg/kg; WT > KO for acute stimulation to 1.5 mg/kg; KO > WT for acute stimulation to 3 and 10 mg/kg	WT = KO for expression of sensitization tested 28 days post acute dose (1, 3 and 10 mg/kg); KO > WT for expression of sensitization when tested 7 days after one acute treatment with the 3 mg/kg dose only				

Table 2 (*continued*)

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Ralph et al. (1999)	D_4R (dopamine D4 receptor)	WT, KO	129/Ola Hsd E14TG2A ES cells × C57BL/6J F2 hybrid	M/F	d-Amphetamine sulfate	10 mg/kg					KO > WT for baseline % PPI; WT = KO for depressant effect of amphetamine on % PPI	
Budygin et al. (2004)	DAT (dopamine transporter)	WT, KO	129/SvJ E14G2a ES cells, 129/SvJ × C57BL/6J hybrid	NS	d-Amphetamine	2.5 and 5 mg/kg (× 2 days or 4 days, once per day)			For 5 mg/kg with 4 conditioning trials: WT = KO in first test, but KO > WT for duration of CPP across repeated tests; For 5 mg/kg with 2 conditioning trials: KO > WT			
Gainetdinov et al. (1999)	DAT	WT, KO	129/SvJ E14G2a ES cells, 129/SvJ × C57BL/6J hybrid	NS	Amphetamine	2 mg/kg	KO > WT for baseline locomotion; WT showed stimulation, whereas KO showed locomotor depression to acute treatment					
Zhuang et al. (2001)	DAT	WT and DAT knock-down	129/SvJ ES cells, 129/SvJ × C57BL6/J	NS	Amphetamine [S(+)-α-methylphenylethyl-amine sulfate]	1, 2, and 3 mg/kg	Dose-dependent increase in locomotor activity in WT mice, but dose-dependent decreased in locomotor activity in the mutant					
Spielewoy et al. (2001)	DAT	WT, HET, KO	129/SvJ E14G2a ES cells, 129/SvJ × C57BL/6J hybrid, N12 backcross to C57BL/6	M/F	d-Amphetamine sulfate	0.3, 1, 3, and 10 mg/kg for acute activity; 1 mg/kg (× 8, once per day) for sensitization development, 0.5 mg/kg for expression of sensitization after 2 days abstinent	WT < HET < KO for baseline activity; WT stimulated only at 3 mg/kg; HET showed locomotor depression at 1 mg/kg and stimulation at 10 mg/kg; KO exhibited locomotor depression at 1, 3 and 10 mg/kg (no stimulation above baseline)	WT exhibited development and expression of sensitization; for HET and KO, the 1 mg/kg amphetamine dose depressed locomotion and there was no significant tolerance or senstization		WT > HET = KO (10 mg/kg, but not 1 mg/kg)		
Giros et al. (1996)	DAT	WT, HET, KO	129/SvJ E14G2a ES cells, 129/SvJ × C57BL/6J hybrid	NS	d-Amphetamine	10 mg/kg	WT = HET < KO for baseline locomotion; WT = HET > KO for acute locomotor response					
Huotari et al. (2004)	COMT (catechol-O-methyltransferase)	WT, HET, KO	129/Sv A7 ES cells, 129/Sv × C57BL/6J hybrid, N4 backcross to C57BL/6J	M/F	d-Amphetamine	2.5, 5, and 10 mg/kg	Both sexes WT = HET = KO (2.5 and 5 mg/kg); at 10 mg/kg male KO > WT or HET, female WT = HET = KO for acute stimulation					

Nabeshima et al. (1994)	TH (tyrosine hydroxylase transgenic [human])	Non-TG, TG	C57BL/6J	M/F	Methamphetamine	0.5 mg/kg once then 2.5 mg/kg (× 14, once per day) beginning 3 days later	Non-TG = TG for baseline locomotion; non-Tg = Tg (0.5 mg/kg; no stimulation); non-Tg > Tg for stimulation to 2.5 mg/kg	No sensitization was seen in either genotype					
Nishii et al. (1998)	TH (tyrosine hydroxylase; expression of TH was rescued in TH KO mice, creating a TG rescue specifically for adrenaline and noradrenaline, but not dopamine)	WT, KO, TG rescue	C57BL/6J × MCH(ICR) hybrid; human TH type 1 gene; backcross to C57BL/6J	NS	Methamphetamine	3 mg/kg	WT > TG rescue for baseline locomotion; WT > TG rescue for acute stimulation						WT = TG rescue for survival rate; KO normal at birth, death by P30
Wang et al. (1997)	VMAT2 (vesicular monoamine transporter 2)	WT, HET	129/SvJ RW4 ES cells; 129/SvJ × C57BL/6J hybrid	M/F	Amphetamine	0.5 mg/kg	HET = WT for baseline locomotion; HET > WT for acute stimulation						KO lethal within 2 week of birth
Takahashi et al. (1997)	VMAT2 (vesicular monoamine transporter 2)	WT, HET	129/SvEv AB1 ES cells; 129/SvEv × C57BL/6J hybrid	NS	Amphetamine	1 and 3 mg/kg once for locomotor activity, twice per day on 2 days for CPP	HET = WT for baseline locomotion; HET > WT for acute stimulation (1 mg/kg, but not 3 mg/kg)		WT > HET (1 and 3 mg/kg)				KO lethal within 2 week of birth
Svenningsson et al. (2003)	DARPP-32	WT, KO	129/Ola E14 ES cells, 129/Ola × C57BL/6 hybrid	NS	d-Amphetamine	7.5 mg/kg for PPI; 2.5 mg/kg for stereotypy				WT > KO	WT > KO for depressant effect of amphetamine on % PPI		
Couceyro et al. (2005)	CART (cocaine- and amphetamine-regulated transcript)	WT, KO	129/Sv RW4 ES cells, 129/Sv × Black Swiss hybrid	M	d-Amphetamine	1, 3, and 6 mg/kg (× 12, once per day) for development of sensitization; 0.3 and 1 mg/kg (× 4, once per day) for CPP	WT = KO for baseline locomotion; KO > WT for acute stimulation (6 mg/kg, but not 1 and 3 mg/kg)	WT > KO for development of sensitization	WT > KO (0.3 mg/kg, but not 1 mg/kg)	WT > KO for stereotypic grooming and head bobbing after acute amphetamine (6 mg/kg, but not 1 and 3 mg/kg)		WT > KO for acute amphetamine induced rearing and sensitization of rearing (6 mg/kg, but not 1 and 3 mg/kg)
Moffett et al. (2006)	CART (cocaine- and amphetamine-regulated transcript)	WT, KO	Unclear	NS	Amphetamine	1, 2, 4, and 8 mg/kg; each mouse received each dose once in random order	WT = KO for baseline locomotion; WT = KO for acute stimulation						
Siuciak et al. (2006)	PDE10A (phosphodiesterase 10A-highly expressed by the medium spiny projection neurons of the striatum)	WT, KO	DBA/1LacJ ES cells, injected into C57BL/6J blastocysts, then male chimeras bred to DBA/1LacJ females	M	Methamphetamine hydrochloride	0.56, 1, and 1.78 mg/kg	KO = WT for acute stimulation						

Table 2 (*continued*)

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Siuciak et al. (2006)	PDE10A	WT, KO	DBA/1LacJ ES cells, injected into C57BL/6J blastocysts, then male chimeras bred to DBA/1LacJ females	M	Amphetamine sulfate	1, 1.78, and 3.2 mg/kg	KO = WT for acute stimulation					
van den Buuse et al. (2005a)	$G\alpha_z$ (inhibitory G-protein [dopamine-related] z, alpha subunit)	WT, KO	C57BL/6 ES cells, pure C57BL/6	M	Amphetamine	1 and 3 mg/kg for activity; 5 mg/kg for PPI	WT = KO for baseline locomotion; KO > WT for acute stimulation (1 and 3 mg/kg)				WT = KO for baseline startle magnitude and % PPI; KO > WT for depressant effect of amphetamine on % PPI	

Legend: CPP = conditioned place preference; GENO = genotype; HET = heterozygous; KO = knockout; NS = not specified; PPI = prepulse inhibition; TG = transgenic; WT = wildtype.

Table 3
Glutamate- and glycine-related single-gene mutant studies using methamphetamines and amphetamines

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Miyamoto et al. (2004b)	GluRε1 (glutamate receptor epsilon 1 subunit)	WT, KO	TT2 (C57BL/6 × CBA F1 hybrid) into ICR mice crossed to C57BL/6; in 2004, "99.99% pure C57BL/6 genetic background"	NS	Methamphetamine hydrochloride	0.3, 1, and 2 mg/kg for acute locomotion; 1 and 2 mg/kg (× 7, once per day) for development of sensitization; 1 and 2 mg/kg (× 3) for CPP	WT > KO for acute stimulation (0.3, 1 and 2 mg/kg)	WT > KO (1 mg/kg), WT = KO (2 mg/kg)	WT = KO (1 and 2 mg/kg)			
Mao et al. (2001)	mGluR1 (metabotropic glutamate receptor 1)	WT, KO	129/Sv HM1 ES cells, 129/Sv × C57BL/6 hybrid	M	d-Amphetamine sulfate	1, 4, and 12 mg/kg	KO > WT for "behavioral responses" (8-point scale that included locomotor activity, stereotypies, sedation, sleep/inactive, and seizures/dyskinesias; 4 and 12 mg/kg); WT = KO at 1 mg/kg					
Mead and Stephens (2003)	GluR2 (glutamate receptor 2)	WT, KO	129/Sv R1 ES cells, 129/Sv × CD-1	M/F	Amphetamine	0.5 mg/kg						WT > KO for effect of amphetamine on conditioned responding; however, WT < KO for initial conditioned responding after saline
Miyamoto et al. (2004a)	NR1 (NMDA receptor NR1 subunit)	WT, KD (knockdown)	129/Ola E14TG2A ES cells, 129/Ola × C57BL/6 × DBA/2 hybrid	M/F	Amphetamine	2 and 4 mg/kg	WT < KD for baseline activity, WT = KD for acute stimulation to 2 mg/kg, WT > KD for acute stimulation to 4 mg/kg			KD > WT for number of "fine movements" at some times (specific measure unclear)		

Table 3 (*continued*)

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Heusner and Palmiter (2005)	NR1 (NMDA receptor NR1 subunit TG with reduced function only in dopamine D1 receptor-containing cells)	Non-TG, TG	129/Sv × C57BL/6 hybrid	NS	Amphetamine	3 and 5 mg/kg	Non-TG = TG for baseline activity; non-TG = TG for acute stimulation			Non-TG = TG for stereotyped behaviors (data not shown)		
Tappe and Kuner (2006)	Homer-1a striatum-specific expression TG	Non-TG, TG	N5-N6 backcross to C57BL/6	NS	Amphetamine	4 mg/kg	TG > non-TG for acute stimulation					
Szumlinski et al. (2005)	Homer-1	WT, KO	CMV-Cre (BALB/cJ) × Flpe (C57BL/6J × 129 × 1/SvJ) × C57BL/6J hybrid	M/F	Methamphetamine	0.3, 1, and 3 mg/kg	KO > WT after 0.3 and 1 mg/kg, but difference was comparable to baseline difference					
Szumlinski et al. (2005)	Homer-2	WT, KO	129 × 1/SvJ × C57BL/6J F5–F10 hyrid	M/F	Methamphetamine	0.3, 1, and 3 mg/kg	KO > WT for acute stimulation (0.3 and 1 mg/kg)					
Tsai et al. (2004)	GlyT1 (glycine transporter 1)	WT, HET	129/SvJ ES cells, injected into C57BL/6 blastocyst, N9 backcross to 129S6/SvEvTac	NS	d-Amphetamine	0.1, 0.32, 1.0, and 3.2 mg/kg (for locomotor activity); 1.0 and 3.2 mg/kg (for PPI)	WT = HET for baseline activity and acute stimulation				WT = HET for baseline% PPI; WT > HET for depressant effect of amphetamine on % PPI (3.2 mg/kg)	KO lethal

See Table 2 for legend.

Table 4
Noradrenergic-related studies of single-gene mutant mice using methamphetamines and amphetamines

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Weinshenker et al. (2002)	Dbh (dopamine beta-hydroxylase)	HET, KO (HET have normal catecholamine levels and are indistinguishable from WT)	129/SvEv AB1 ES cells, 129/SvEv × C57BL/6J hybrid	NS	Amphetamine	1, 2, 3, 5, and10 mg/kg for acute; 2 mg/kg (× 6, once per day) for development of sensitization; 2 mg/kg expression test on day 8, 15, and 43	KO > HET (2 mg/kg); HET > KO (5 mg/kg); HET = KO (1 and 3 mg/kg) for acute stimulation	HET > KO for development and expression of sensitization		KO > HET (acute at 5 mg/kg)		
Xu et al. (2000a)	NET (norepinephrine transporter)	WT, KO	129/SvJ AK7 ES cells; 129/SvJ × C57BL/6J hybrid	M	Amphetamine	1 mg/kg	KO > WT for acute stimulation					
Auclair et al. (2002)	α_{1B}-AR (alpha 1B adrenoceptor)	WT, KO	129/Sv HM1 ES cells, 129/Sv × C57BL/6J hybrid	M	d-Amphetamine sulfate	3 and 6 mg/kg	WT > KO for acute stimulation (3 and 6 mg/kg)					
Drouin et al. (2002)	α_{1B}-AR (alpha 1B adrenoceptor)	WT, KO	129/Sv HM1 ES cells, 129/Sv × C57BL/6J hybrid	M	d-Amphetamine sulfate	1, 2, and 3 mg/kg for acute stimulation; 1 and 2 mg/kg (× 5, every other day) for sensitization development, then 1 and 2 mg/kg for expression of sensitization 10 days later	WT = KO for baseline locomotion; WT > KO for acute stimulation (2 and 3 mg/kg)	WT > KO for development and expression of sensitization (1 and 2 mg/kg)				
Battaglia et al. (2003)	α_{1B}-AR (alpha 1B adrenoceptor)	WT, KO	129/Sv HM1 ES cells, 129/Sv × C57BL/6J hybrid	M	(+)-Methamphetamine	5 mg/kg (× 3 at 2 h intervals)	WT = KO for acute response	WT > KO				WT = KO for hyperthermia
Auclair et al. (2004)	α_{1B}-AR (alpha 1B adrenoceptor)	WT, KO	129/Sv HM1 ES cells, 129/Sv × C57BL/6J hybrid	M	d-Amphetamine sulfate	2 mg/kg (× 6, once per day) for sensitization development	WT > KO for acute stimulation	WT > KO for sensitization on day 6				
Sadalge et al. (2003)	α_{1D}-AR (alpha 1D adrenoceptor)	WT, KO	129/SvTac ES cells, 129/SvTac × C57BL/6 hybrid	NS	d-Amphetamine	2 mg/kg	WT > KO for acute stimulation					

Table 4 (*continued*)

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Juhila et al. (2005)	α_{2A}-AR (alpha 2A adrenoceptor)	KO, WT	129/Sv R1 ES cells, $\geqslant$ N5 backcross to C57BL/6J	M	d-Amphetamine sulfate	5 mg/kg for acute; 2 mg/kg ($\times$ 4, once per day) for development of sensitization; 2 mg/kg expression test after a 2 day break; 2 and 4 mg/kg ($\times$ 3, once every other day) for CPP	KO > WT for acute increase in ambulatory activity and speed (5 mg/kg); WT = KO for number of entries into the central area (5 mg/kg)	WT $\geqslant$ KO for expression of sensitization (2 mg/kg)	KO = WT (2 and 4 mg/kg)			
Lahdesmaki et al. (2004)	α_{2A}-AR (alpha 2A adrenoceptor)	WT, KO	129/Sv R1 ES cells, N5 backcross to C57BL/6J	M/F	d-Amphetamine sulfate	10 mg/kg					WT $\leqslant$ KO for baseline % PPI and startle magnitude after saline; KO > WT for depressant effect of drug on % PPI; KO > WT for increase in startle magnitude by drug	
Sallinen et al. (1998)	α_{2C}-AR (alpha 2C adrenoceptor)	WT, KO	129/Sv ES cells, 129/Sv $\times$ C57BL/6J hybrid bred to C57BL/6J $\times$ DBA/2J F1; backcrossed to C57BL/6J for "several generations"	M/F	d-Amphetamine sulfate	2 mg/kg	WT = KO for baseline locomotion (both M and F); KO > WT for acute stimulation (M only)					
Sallinen et al. (1998)	α_{2C}-AR (alpha 2C adrenoceptor; overexpression)	Non-TG, TG	FVB/N	F	d-Amphetamine sulfate	2 mg/kg	Non-TG = TG for baseline locomotion; non-TG > TG for acute stimulation					

See Table 2 for legend.

Table 5
Cell support and signaling-related protein studies in single-gene mutant mice using methamphetamines and amphetamines

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Herve et al. (2001)	$G\alpha_{olf}$ (G-protein alpha, olfactory isoform)	WT, HET	129/Sv ES cells, 129/Sv × C57BL/6 hybrid	M	d-Amphetamine	1, 2, and 3 mg/kg	WT > HET for acute response (1, 2 and 3 mg/kg), but also following saline injection					
Gainetdinov et al. (2003)	GRK6 (G protein-coupled receptor kinase 6)	WT, HET, KO	129/SvJ AK7 ES cells, 129/SvJ × C57BL/6J hybrid	M/F	d-Amphetamine	3 mg/kg	KO = HET > WT for acute stimulation					
Beaulieu et al. (2005)	βArr2 (beta-arrestin 2)	WT, KO	129/SvJ ES cells, 129/SvJ × C57BL/6J hybrid	NS	Amphetamine	2 and 3 mg/kg	KO < WT for acute stimulation			KO = WT for stereotypy time		
Reed et al. (2002)	PDE1B (phosphodiesterase 1B)	WT, HET, KO	129/SvJ E14TG2a ES cells, 129/SvJ × C57BL/6J hybrid, N3 backcross to C57BL/6J	M/F	d-Methamphetamine hydrochloride	1 mg/kg	Activity counts: KO > WT = HET for baseline; KO > WT = HET after d-methamphetamine Total Distance: female KO > WT = HET for both baseline and after drug; male KO = HET = WT for baseline and male KO > HET > WT after drug					
Brandon et al. (1998)	RIIβ-PKA (protein kinase A RII beta isoform)	WT, KO	129/SvJ × C57BL/6 hybrid	NS	d-Amphetamine	10 mg/kg for acute; 2.5 and 5 mg/kg (× 5, once per day) for development of sensitization	WT = KO for acute stimulation (10 mg/kg)	KO > WT for development of sensitization (2.5 and 5 mg/kg)				
Beaulieu et al. (2004)	GSK-3β (glycogen synthase kinase 3 beta)	WT,HET	129/J ES cells, 129/J × C57BL/6J hybrid	NS	Amphetamine	1 and 2 mg/kg	WT = HET for baseline; WT > HET for acute stimulation					
Biala et al. (2005)	Calcineurin overexpression; forebrain specific	non-TG, TG	C57BL/6J × CBA/J hybrid, > N10 backcross to C57BL/6J	NS	d-Amphetamine sulfate	1, 2, 5, and 10 mg/kg for acute; 2 mg/kg (× 5, once every 3 days) for development of sensitization; 2 mg/kg, 7 days later for sensitization expression; 2 mg/kg (× 4, once every 2 days) for CPP	Non-TG = TG for baseline locomotion; non-TG = TG for acute locomotor response (all doses)	Non-TG > TG for development and expression of sensitization	Non-TG > TG			

Table 5 (*continued*)

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Tanaka et al. (2006)	Adcyap1 (pituitary adenylate cyclase-activating polypeptide 1)	WT, KO	129/Ola E14tg2a ES cells, 129/Ola × C57BL/6 hybrid, N5 backcross to ICR	NS	Amphetamine	2 mg/kg for activity; 2 and 10 mg/kg for PPI; 1 and 2 mg/kg for jumping behavior	KO > WT for baseline locomotion; WT stimulated by amphetamine, KO showed locomotor depression to amphetamine				KO < WT for baseline % PPI; KO = WT for startle magnitude; little effect of amphetamine on PPI	Jumps: KO > WT at baseline; amphetamine reduced explosive jumping in KO
Shaldubina et al. (2007)	SMIT1 (sodium-dependent myo-inositol cotransporter 1)	WT, HET	129/SvJ X1 ES cells, 129/SvJ × C57BL/6 hybrid	NS	d-Amphetamine	3 mg/kg	WT = HET for acute stimulation					
Pillai-Nair et al. (2005)	NCAM-EC (neural cell adhesion molecule extracellular region overexpression)	non-TG, TG	C57BL/6	M/F	Amphetamine	2 and 4 mg/kg	TG > non-TG for baseline locomotion; TG > non-TG for acute stimulation (4 mg/kg only)					
Dluzen et al. (2001)	BDNF (brain derived neurotrophic factor)	WT, HET	129/Sv J1 ES cells, 129/Sv × Balb/c hybrid	NS	Amphetamine	5 mg/kg	HET > WT for effect of amphetamine on number of movements			WT = KO for stereotypy counts		
Pineda et al. (2005)	Double HTT/BDNF (huntingtin is expressed and brain-derived neurotrophic factor is knocked out)	WT_{BDNF}/WT_{HTT}, WT_{BDNF}/TG_{HTT}, HET_{BDNF}/WT_{HTT}, HET_{BDNF}/TG_{HTT}	BALB/c × C6CBA hybrid	NS	Amphetamine	5 mg/kg	$HET_{BDNF}/WT_{HTT} > WT_{BDNF}/WT_{HTT} = WT_{BDNF}/TG_{HTT} > HET_{BDNF}/TG_{HTT}$ for acute stimulation					
Skelton et al. (2003)	PTPα (protein tyrosine phosphatase alpha)	WT, KO	129/SvEv × Black Swiss intercross	M/F	d-Methamphetamine hydrochloride	1 mg/kg	WT = KO for acute stimulation					WT = KO for rearing
Kholodilov et al. (2004)	GDNF (glial derived neurotrophic factor overexpression)	Non-TG, TG	CBA × C57BL/6 backcross to C57BL/6	M/F	Amphetamine	2 mg/kg	Non-TG = TG for baseline locomotion, TG > non-TG for acute stimulation					

Borgkvist et al. (2006)	OTX2 (orthodenticle homolog 2; has a critical role in brain developoment)	WT, KO	129/Sv R1 ES cells, 129/Sv × C57BL/6 × DBA/2 hybrid	NS	Amphetamine sulfate	10 mg/kg	WT = KO for baseline locomotion; KO > WT for acute stimulation	
Eilam et al. (1998)	ATM (ataxia-telangiectasia gene; encodes a protein kinase with a PI-3 kinase-related domain)	WT, KO	129/SvEv TC-1 ES cells, 129/SvEv × Black Swiss × C57BL/6J hybrid	M	d-Amphetamine sulfate	5 and 10 mg/kg	KO > WT (data appear to be collapsed on dose)	
Sieber et al. (2004)	EphA5 (ephrin A5 receptor overexpression)	Non-TG, HET, TG	C57BL/6 × CBA hybrid	M/F	Amphetamine sulfate	0.5, 1.5, 4.5, and 10 mg/kg	Non-TG = HET = TG for baseline locomotion, Non-TG = HET > TG for acute stimulation (1.5 mg/kg), Non-TG > TG (4.5 mg/kg, HET not tested), non-TG = TG (0.5 and 10 mg/kg, HET not tested)	
Flores et al. (2005)	DDC (deleted in colorectal cancer; aka netrin receptor)	WT, HET	129/Sv D3 ES cells, maintained on 129/Sv background	M	d-Amphetamine sulfate	1.5, 2.5, and 4 mg/kg for acute; 4 mg/kg (× 5, every other day) for development of sensitization; 2 mg/kg expression test 1 week later	WT > HET for acute stimulation (1.5, 2.5 and 4 mg/kg)	WT > HET for expression of sensitization (not tested during development)

See Table 2 for legend.

Table 6
Methamphetamine and amphetamine studies in steroid- and peptide-related single-gene mutants

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Koks et al. (2003)	CCK_2 (cholecystokinin receptor 2)	WT, KO	129/Sv J1 ES cells, 129/Sv × C57BL/6J hybrid	M	(+/−) Amphetamine	3 and 6 mg/kg	3 mg/kg: WT > KO for locomotion time and distance; WT = KO for corner entries; 6 mg/kg: WT = KO for locomotion time; KO > WT for distance and corner entries					WT > KO for rearing (3 and 6 mg/kg)
Koks et al. (2001)	CCK_2 (cholecystokinin receptor type 2)	WT, HET, KO	129/Sv J1 ES cells, N3 backcross to C57BL/6	M	Amphetamine	3 and 6 mg/kg	3 mg/kg: WT > HET = KO for time in locomotion and distance; WT = HET > KO for corner entries; 6 mg/kg: WT = HET = KO for time in locomotion, KO > WT = HET for distance and corner entries					3 mg/kg: KO < WT = HET for rearing; 6 mg/kg: WT = HET = KO for rearing
Runkorg et al. (2006)	CCK_2 (cholecystokinin receptor 2)	WT, KO	129/Sv J1 ES cells, N10 backcross to C57BL/6	M	Amphetamine sulfate	1 mg/kg (× 4, once per day) for sensitization development; 1, 2, and 3 mg/kg (for CPP)	WT = KO for basal activity; no acute stimulation seen	KO > WT for sensitization on day 4	WT > KO at 2 and 3 mg/kg			
van den Buuse et al. (2005b)	Gastrin (peptide hormone; binds CCK_2 receptor)	WT, KO	Original: 129/Sv R1 ES cells, 129/Sv × C57BL/6 hybrid. Paper says: BALB/c (CrSlc substrain)	M	Amphetamine	5 and 10 mg/kg					WT = KO for baseline % PPI and startle magnitude, WT > KO for depressant effect of 5 mg/kg amphetamine on % PPI, WT = KO at 10 mg/kg	

van den Buuse et al. (2003)	Ar (aromatase)	WT, HET, KO	129/Sv KG-1 ES cells, 129/Sv × C57BL/6J F2 hybrid	M/F	Amphetamine	5 mg/kg	For acute stimulation at 1 month of age WT = HET = KO; at 12–18 months of age male KO > WT, but female KO = HET = WT		WT = HET = KO at 1 and 12–18 months	
Brun et al. (2005)	STOP (stable tubule only polypeptide)	WT, KO	129/SvPas ES cells, possible pure 129/SvPas or hybrid 129/SvPas × BALB/c (unclear)	M	d-Amphetamine sulfate	1, 3, and 5 mg/kg	KO > WT for acute stimulation (1, 3 and 5 mg/kg)			
Smith et al. (2005)	MCH1R (melanin-concentrating hormone 1 receptor)	WT, KO	129/SvEv ES cell, 129/SvEv × C57BL/6 hybrid	M	d-Amphetamine	1, 2, and 3 mg/kg	WT = KO (1 mg/kg); KO > WT (2 and 3 mg/kg) for acute stimulation			
Kuo et al. (2002)	NPY (neuropeptide Y overexpression, CNS specific)	non-TG, TG	C57BL/6 × DBA/2 hybrid	M	Amphetamine	4 and 8 mg/kg				Non-TG > TG for sensitivity to anorectic effect of amphetamine
Steckler and Holsboer (2001)	GR (glucocorticoid receptor [rat] knockdown)	non-TG, TG	C57BL/6 × C3 H hybrid	M	d-Amphetamine sulfate	4 mg/kg (× 10, once per day in test chamber or in home cage) for sensitization development; 4 mg/kg expression test 48 h later	TG > non-TG for baseline locomotion; they habituated to a similar level of baseline behavior across several days. Initial sensitivity to amphetamine not measured.	Non-TG > TG in activity after amphetamine during sensitization development period (some sensitization in non-TG, but reduced activation across days in TG); similar results for expression of sensitization, where context-dependent sensitization was seen in non-TG and tolerance was seen in TG	TG > non-TG for stereotypy after amphetamine (no effect of context)	TG > non-TG for baseline rearing; TG > non-TG for amphetamine-increased rearing
Cyr et al. (2001)	GR (glucocorticoid receptor antisense construct)	non-TG, TG	C57BL/6 × C3H hybrid	M/F	Amphetamine	2 mg/kg	TG > non-TG for locomotion after amphetamine, but no baseline behavior measured			
Soderpalm et al. (1999)	bGH (bovine growth hormone overexpression)	Non-TG, TG	C57BL/6 × CBA	M	d-Amphetamine	1 mg/kg	TG > non-TG for baseline locomotion, week 1, no treatment, but TG = non-TG for locomotion, week 2 after saline challenge; TG > non-TG for acute stimulation			

See Table 2 for legend.

Table 7
Single-gene mutant studies using methylphenidate

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Siesser et al. (2006)	TRβ (β1 thyroid receptor [human] transgenic; pituitary specific)	non-TG, TG	TRβ (αGSU), N12 backcross to C57BL6/NIH	M/F	Methylphenidate hydrochloride	40 mg/kg	Male non-TG = TG for initial baseline locomotion, but TG > WT for locomotion over habituation sessions; females reported as not different, but appear more active after saline in figure. Male non-TG > TG for locomotor stimulant response to methylphenidate; female largely unresponsive to methylphenidate					
Siesser et al. (2005)	TRβ (β1 thyroid receptor [human] knockin)	WT, HET (TRβ+/−), KI (TRβ+/+)	129/Sv TC-1 ES cells, 129/Sv × Black Swiss hybrid	M/F	Methylphenidate	5, 10, and 30 mg/kg	WT = HET = KI for initial baseline locomotion; male KI = HET > WT for locomotion over habituation sessions (females not different)					Vigilance task: Male WT = HET > KI for dose-dependent impairment in vigilance task by methylphenidate, female WT = HET = KI
Scearce-Levie et al. (1999a)	5-HT$_{1B}$ (serotonin 1B receptor)	WT, KO	129/SvPas × 129/Sv-ter × 129/SvEvTac hybrid	NS	Methylphenidate	10 mg/kg	WT = KO for baseline locomotion; KO > WT for acute stimulation					
Tanaka et al. (2006)	Adcyap1 (pituitary adenylate cyclase-activating polypeptide 1)	WT, KO	129/Ola E14tg2a ES cells, 129/Ola × C57BL/6 hybrid, N5 backcross to ICR	NS	Methylphenidate	10 and 30 mg/kg for jumping behavior						Jumps: KO > WT at baseline; methylphenidate reduced explosive jumping in KO
Yamashita et al. (2006)	DAT	WT, KO	129/SvJ J1 ES cells, 129/SvJ × C57BL/6J hybrid	M	Methylphenidate hydrochloride	30 and 60 mg/kg					WT > KO for baseline PPI; Methylphenidate reduced PPI in WT (30 and 60 mg/kg), but enhanced PPI in KO (60 mg/kg)	

Gainetdinov et al. (1999)	DAT	WT, KO	129/SvJ E14G2a ES cells, 129/SvJ × C57BL/6J hybrid	NS	Methylphenidate	30 mg/kg	KO > WT for baseline locomotion; WT showed stimulation, whereas KO showed locomotor depression to acute treatment				
Sora et al. (1998)	DAT	WT, HET, KO	129/SvJ J1 ES cells, 129/SvJ × C57BL/6J hybrid	NS	Methylphenidate hydrochloride	5 mg/kg (× 2, once per day)		WT = HET = KO			
Umemori et al. (2003)	Lyn (Src-family non-receptor protein tyrosine kinase)	WT, KO	129/Ola ES cells, 129/Ola × C57BL/6 hybrid	NS	Methylphenidate	5 mg/kg	KO < WT for baseline locomotion; KO = WT for acute stimulation				
Ihalainen et al. (2001)	α_{2C}-AR (alpha 2C adrenoceptor)	WT, KO	129/Sv R1 ES cells, (129/Sv × C57BL/6J) × (C57BL/6J × DBA/2J) or × FVB/N (unclear which background used here)	F	Methylphenidate hydrochloride	0.3, 1, and 3 mg/kg (mice were tested 3 times at each drug dose and saline, with 3 days between tests)					Cue discrimination: WT > KO for dose-dependent reduction in total responses, but baseline also higher; WT > KO for % correct responses overall; WT > KO for dose-dependent reduction in collected rewards, but baseline also higher
Hess et al. (1996)	Cm (coloboma mutant)	HET, WT	Mutation identified on C3H/HeH × 101/H F1, then N32 backcross to C57BL/6By, then N10 backcross to C3H/HeSnJ	M/F	Methylphenidate hydrochloride	2, 4, 8, and 32 mg/kg (× 1 for each dose tested, with 7 days between doses)	HET > WT for locomotion after saline, HET = WT for acute stimulation (all doses)			*Cm*/+ = WT	

See Table 2 for legend.

Table 8
Single-gene mutant studies using MDMA (methylenedioxymethamphetamine), also known as *ecstasy*

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Itzhak et al. (2004)	nNOS (neuronal nitric oxide synthase)	WT, KO	129/Sv J1 ES cells, 129/Sv × C57BL/6 hybrid	M	(+/−) MDMA hydrochloride	10 mg/kg (× 6, once per day on days 1–5 and on day 45)	WT = KO for acute stimulation	WT = KO for sensitization development; WT > KO for expression of sensitization				
Dulawa et al. (2000)	5-HT_{1B} (serotonin 1B receptor)	WT, KO	129/SvPas × 129/Sv-ter × 129/SvEvTac hybrid	M	(+)MDMA	10 mg/kg					WT = KO for baseline startle magnitude and % PPI; KO < WT for depressant effect of MDMA on startle magnitude; KO > WT for increased % PPI by MDMA	
Scearce-Levie et al. (1999b)	5-HT_{1B} (serotonin 1B receptor)	WT, KO	129/SvPas × 129/Sv-ter × 129/SvEvTac hybrid	M	MDMA hydrochloride	3.3, 10, and 30 mg/kg	WT = KO for baseline locomotion; WT > KO for acute stimulation (10 and 30 mg/kg)			KO < WT for MDMA-induced stereotypy (30 mg/kg)		WT = KO in depressant effect of MDMA on rearing and nose pokes (3.3, 10, and 30 mg/kg)
Scearce-Levie et al. (1999a)	5-HT_{1B} (serotonin 1B receptor)	WT, KO	129/SvPas × 129/Sv-ter × 129/SvEvTac hybrid	NS	MDMA	3.3 and 30 mg/kg	WT = KO for baseline locomotion; WT > KO for acute stimulation					WT = KO for baseline rearing and depression of rearing by MDMA; WT = KO for baseline exploratory nose pokes and depression of nose pokes by MDMA
Bengel et al. (1998)	5-HTT (serotonin transporter)	WT, HET, KO	129/Sv R1 ES cells, 129/Sv × C57BL/6J × CD-1 hybrid and 129/Sv × C57BL/6J hybrid	M	(+)MDMA hydrochloride	5 mg/kg					WT = HET = KO for baseline locomotion; WT > HET > KO for acute stimulation	

Robledo et al. (2004)	μ-opioid receptor	WT, KO	129/Sv ES cells, 129/ Sv × C57BL/6 hybrid, > N10 backcross to C57BL/6	M/F	MDMA hydrochloride	10 mg/kg (× 4, once every other day)		KO = WT
Risbrough et al. (2006)	$D_{1A}R$ (dopamine D1A receptor)	WT, KO	129/Sv J1 ES cells, 129/ Sv × C57BL/6 hybrid, N10-12 C57BL/6J	M/F	(+/−) MDMA	20 mg/kg	Male and female KO > WT for acute stimulation	
Risbrough et al. (2006)	D_2R (dopamine D2 receptor)	WT, KO	129/Sv D3 ES cells, 129/ Sv × C57BL/6J, N17 backcross to C57BL/6J	M/F	(+/−) MDMA	20 mg/kg	Male KO < WT; female KO = WT	
Risbrough et al. (2006)	D_3R (dopamine D3 receptor)	WT, KO	129/Sv J1 ES cells, 129/ Sv × C57BL/6, N10-12 backcross to C57BL/6J	M/F	(+/−) MDMA	20 mg/kg	Female KO < WT for acute stimulation; male KO = WT	
Powell et al. (2004)	DAT (dopamine transporter)	WT, KO	129/SvJ E14G2a ES cells, 129/ SvJ × C57BL/6J hybrid	M/F	(+/−) MDMA	20 mg/kg	KO > WT for basal locomotor activity; MDMA increased locomotor activity in WT, but decreased activity in KO	

See Table 2 for legend.

Table 9
Other single-gene mutant studies using methamphetamines and amphetamines

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Wolinsky et al. (2007)	TA1 (trace amine 1 receptor)	WT, KO	129S1/Sv ES cells, 129S1/Sv × C57BL/6J hybrid	M	d-Amphetamine	1, 2.5, and 5 mg/kg	WT = KO for baseline; KO > WT for acute stimulation					WT = KO for baseline rearing; KO > WT for rearing after 1 mg/kg, but KO < WT for rearing after 5 mg/kg amphetamine
Marquez et al. (2007)	μ-Opioid receptor	WT, KO	129/Sv ES cells, 129/Sv × C57BL/6 hybrid, > N10 backcross to C57BL/6	M	Amphetamine	1 mg/kg (× 4, once per day)			WT = KO			
Kas et al. (2004)	μ-Opioid receptor	WT, KO	129/SvEv ES cells, 129/SvEv × C57BL/6J hybrid	F	d-Amphetamine sulfate	4 mg/kg	KO > WT for total distance after amphetamine					
Backman et al. (2003)	Nurr1 (the murine orphan nuclear receptor)	WT, HET	129 ES cells, > N10 backcross to C57BL/6	M	Methamphetamine	5 mg/kg	HET > WT for baseline horizontal activity and total distance, and for both measures after methamphetamine (activation data were not corrected for baseline difference)			HET > WT (assessed in automated Omnitech activity monitors)		HET = WT for baseline rearing; HET > WT for rearing after methamphet-amine
Eells et al. (2002)	Nurr1 (nuclear receptor 1)	WT, HET	129/SvJ J1 ES cells, 129/SvJ × C57BL/6 hybrids	M	Amphetamine	2.5 or 5 mg/kg	WT = HET for total distance and center time in an open field after amphetamine					
Nagai et al. (2005)	tPA (tissue plasminogen activator)	WT, KO	129/Sv D3 ES cells, N12 backcross to C57BL/6J	NS	Methamphetamine hydrochloride	1 and 2 mg/kg (× 5, once per day) for sensitization; (× 3, once per day) for CPP	WT = KO for acute stimulation	WT > KO (1 mg/kg), WT = KO (2 mg/kg)	WT > KO (1 and 2 mg/kg)			
Mori et al. (2002)	Mint-1 (aka X11 and mammalian Lin10; implicated in synaptic vesicle exocytosis)	WT, KO	129/Sv clone put into CCE28 ES cells, 129/Sv × C57BL/6J F2 hybrid	M	Methamphetamine	10 mg/kg				WT > KO		
Kubota et al. (2002)	HDC (histidine decarboxylase)	WT, KO	129/Sv R1 ES cells, 129/Sv × CD-1 hybrid	NS	Methamphetamine	1 mg/kg (× 7, once per day)	KO = WT for baseline; KO > WT for acute stimulation	KO = WT				

Dai et al. (2005)	H_1 (histamine 1 receptor)	WT, KO	129/Ola ES cells, 129/Ola × C57BL/6 hybrid	M	Methamphetamine	1 mg/kg (× 8, every other day)	WT > KO for baseline locomotion				WT > KO for isolation-induced disruption of PPI in mice treated repeatedly with metham-phetamine	
Iwabuchi et al. (2004)	H_1 and H_2 (histamine 1 and 2 receptors)	WT, H1KO, H2KO, DKO	129/Ola ES cells, 129/Ola × C57BL/6 hybrid	NS	Methamphetamine	1 mg/kg (× 7, once per day) for sensitization development	WT = HIKO, WT = H2KO, WT = DKO for acute stimulation	WT = H1KO, WT = H2KO, WT < DKO for sensitization development				
Toyota et al. (2002)	H_3 (histamine 3 receptor)	WT, KO	Gene isolated from 129/Ola genomic library; introduced into stem cells (type not specified); 129/Ola × C57BL/6J F2 hybrid	M	Methamphetamine	1 mg/kg	WT > KO for acute stimulation			WT > KO		
Okabe et al. (2005)	Nociceptin receptor	WT, HET, KO	129/SvJ J1 ES cells, 129/SvJ × C57BL/6J hybrid	M	Methamphetamine hydrochloride	1 mg/kg (× 3, every other day) for development of sensitization; .5 mg/kg expression test 2 week later	WT = HET = KO for baseline locomotion; WT = HET = KO for acute stimulation	WT = HET = KO for both development and expression of sensitization				
Itzhak et al. (2004)	nNOS (neuronal nitric oxide synthase)	WT, KO	129/Sv J1 ES cells, 129/Sv × C57BL/6 hybrid	M	d-Methamphetamine hydrochloride	1 mg/kg (× 6, once per day on days 1–5 and on day 45)	WT = KO for acute stimulation	WT > KO for both development and expression of sensitization				
Itzhak et al. (1998)	nNOS (neuronal nitric oxide synthase)	WT, HET, KO	129/Sv J1 ES cells, 129/Sv × C57BL/6 hybrid	M	d-Methamphetamine hydrochloride	1 mg/kg once, then 5 mg/kg every 3 h; 1 mg/kg sensitization expression test after 3 days off drug	WT = KO for baseline locomotion; WT = KO for acute stimulation (1 mg/kg) (HET not tested)	WT > KO for expression of sensitization (1 mg/kg) (HET not tested)				WT = HET > KO for hyperthermia (5 mg/kg)
Itzhak et al. (2000)	nNOS and iNOS (neuronal and inducible nitric oxide synthase)	WT, nNOSKO, iNOSKO	nNOS: 129/Sv J1 ES cells, 129/Sv × C57BL/6 hybrid iNOS: 129/P2 E14TG2a ES cells, 129/P2 × C57BL/6 hybrid, backcross to C57BL/6	M	Methamphetamine HCl	1 mg/kg once, then 5 mg/kg × 3, every 3 h for sensitization development; 1 mg/kg after 3 days off drug for expression of sensitization	WT = nNOS = iNOS for acute locomotor response (no baseline data given)	WT = iNOS > nNOS for expression of sensitization				

Table 9 (*continued*)

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Coitinho et al. (2002)	$Prnp^{0/0}$ (cellular prion protein, aka Zrch-1)	KO, WT	129/SvEv × C57BL/6J hybrid	NS	Amphetamine	1 mg/kg	WT = KO for acute stimulation					
Bastia et al. (2005)	Forebrain-specific $A_{2A}R$ (adenosine 2A receptor)	WT, KO	129/Sv × C57BL/6 hybrid	NS	Amphetamine	2.5 mg/kg (× 8, once per day) for development of sensitization; 2.5 mg/kg expression test 1 week later	WT = KO for acute stimulation (little initial response in either genotype)	WT > KO for both development and expression of sensitization				
Chen et al. (2003a)	$A_{2A}R$ (adenosine A_{2A} receptor)	WT, KO	129/SvJae ES cells, 129/SvJae × C57BL/6, OR 129/SvJae × 129/SvEvTac (not clear)	NS	Amphetamine	2.5 mg/kg (× 8, once per day) for sensitization development		WT > KO				
Chen et al. (2000)	$A_{2A}R$ (adenosine A_{2A} receptor)	WT, KO	129/SvJae ES cells, 129/SvJae × C57BL/6 hybrid	NS	Amphetamine	2.5 mg/kg	WT > KO for acute stimulation					
Chen et al. (2000)	$A_{2A}R$ (adenosine A_{2A} receptor)	WT, KO	129/SvJae ES cells, 129/SvJae × 129/SvEvTac hybrid	NS	Amphetamine	1.5 and 2.5 mg/kg	WT > KO for acute stimulation (1.5 and 2.5 mg/kg)					
Chen et al. (2003b)	$A_{2A}R$ (adenosine A_{2A} receptor)	WT, KO	129/SvJae ES cells, 129/SvJae × 129/SvEvTac hybrid	M/F	Amphetamine	2.5 and 5 mg/kg (× 8, once per day) for sensitization development; 5 mg/kg expression test 2 week later	WT = KO for acute stimulation (2.5 and 5 mg/kg)	WT > KO for development of sensitization (2.5 and 5.0 mg/kg); WT > KO for expression of sensitization (5 mg/kg)		WT > KO day 1 and 8		
Wang et al. (2003)	$A_{2A}R$ (adenosine A_{2A} receptor)	WT, KO	129/Sv × 129/Sv-CP ES cells, N4 backcross to CD-1	M	Amphetamine	5 mg/kg					WT > KO in baseline startle amplitude and % PPI. No significant disruption of PPI in either WT or KO.	

Reynolds et al. (2003)	GABA-Aα1 (GABA-A receptor alpha-1 subunit)	WT, KO	129/SvEv AB2.2 ES cells; 129/SvEv × C57BL/6 F4 and F5 hybrids	NS	Amphetamine sulfate	0.5, 1, 2.5, 5, and 7.5 mg/kg	WT = KO (0.5, 1 and 2.5 mg/kg), WT > KO (5 and 7.5 mg/kg) for acute stimulation			WT = KO (0.5, 1, 2.5, 5 and 7.5 mg/kg)	
Yee et al. (2005)	GABA-Aα3 (GABA-A receptor alpha-3 subunit)	WT, KO	129/SvJ RW-4 ES cells, 129/SvJ × C57BL/6J × *hACTB:Flp*, N5 backcross to 129/SvJ	M/F	Amphetamine	2.5 mg/kg	WT = KO for acute stimulation				
Resnick et al. (1999)	GABA-Aβ_3 (GABA-A receptor beta-3 subunit)	WT, HET, KO	129/SvJ R1 ES cells, 129/SvJ × C57BL/6J hybrid	M	Amphetamine	5 mg/kg	WT = HET > KO for acute stimulation				
Houchi et al. (2005)	CB_1 (cannabinoid 1 receptor)	WT, KO	129/Sv R1 ES cells, 129/Sv × CD1, ⩾ N5 backcross to CD1	M	d-Amphetamine	1.2, 2.4, and 5 mg/kg	WT = KO for acute stimulation				
Cossu et al. (2001)	CB_1 (cannabinoid 1 receptor)	WT, KO	129/Sv R1 ES cells, 129/Sv × CD1, ⩾ N5 backcross to CD1	M	d-Amphetamine sulfate	0.1 mg/kg per self-administered tail vein injection					Self-administration: WT = KO for number of nose-pokes for drug infusion
Abeliovich et al. (2000)	α-Syn (alpha synuclein)	WT, KO	129/SvJ GS ES cells; 129/SvJ × C57BL/6 F2 hybrid	M/F	d-Amphetamine sulfate	4 mg/kg	WT > KO for acute stimulation				
Fleming et al. (2006)	α-synuclein (alpha synuclein [human] overexpression TG; Thy-1 promoter)	Non-TG, TG	C57BL/6 × DBA/2 F1 hybrid, N1 backcross to DBA/2	M	Amphetamine	5 mg/kg	Non-TG = TG for rears, forelimb steps and hindlimb steps after vehicle. Non-TG > TG for amphetamine-induced increase in forelimb steps.			Stereotyped Behaviors: Non-TG > TG after vehicle, and for increased stereotypy after amphetamine Grooming: non-TG > TG for grooming after vehicle and for amphetamine-induced decrease	Balance beam: TG > non-TG for baseline errors/step; no effect of amphetamine on errors. Non-TG = TG for number of steps. Non-TG > TG for amphetamine-induced increase in speed to traverse beam
Richfield et al. (2002)	hα-SYN (human alpha synuclein, dopamine neuron specific)	Non-TG, hwα-TG (human wildtype SYN gene), hm2α-TG (human mutated SYN gene)	C57BL/6	M/F	Amphetamine	0.375 mg/kg (once on day 1 and once on day 7); 1 mg/kg (biweekly × 6 then challenged 1 week later)	Non-TG = hwα-TG = hm2α-TG for baseline locomotion, no acute stimulant response (0.375 mg/kg)	hm2α-TG < non-TG < hwα-TG (0.375 mg/kg) and hm2α-TG < non-TG = hwα-TG (1 mg/kg) for sensitization expression			

Table 9 (*continued*)

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Ishiguro et al. (2006)	NrCAM (neural cell adhesion molecule)	WT, HET, KO	C57BL/6 × 129 hybrid	NS	Amphetamine	2 mg/kg (× 2, once per day)			WT = HET > KO			
Eilam et al. (1998)	ATM (the gene that causes ataxia-telangiectasia in humans)	WT, KO		M	d-Amphetamine sulfate	5 and 10 mg/kg	KO > WT (data appear to be collapsed on dose)					
Marazziti et al. (2004)	GPR37 (an orphan G protein-coupled receptor)	WT, KO	129P2/OlaHsd E14.1 ES cells, 129P2/OlaHsd C57BL/6J hybrid	M	d-Amphetamine sulfate	4 mg/kg	KO > WT for acute stimulation					
Kim et al. (2005)	DJ-1 (PARK7; linked to Parkinson's disease)	WT, KO	129/Ola E14K ES cells, N7 backcross to C57BL/6	NS	Amphetamine	2 mg/kg	WT > KO for acute stimulation					
Labarca et al. (2001)	α4 nAChR (alpha 4 nicotinic acetylcholine receptor)—a point mutation that created hypersensitivity of the receptor	WT, HET	129/SvJ ES cells, 129/ SvJ × C57BL/6 hybrid	NS	d-Amphetamine sulfate	5 mg/kg	WT = HET for baseline locomotion; WT = HET for acute stimulation					
Orb et al. (2004)	α4 nAChR (alpha 4 nicotinic acetylcholine receptor)-a point mutation that created hypersensitivity of the receptor	WT, HET	129/SvJ ES cells, 129/ SvJ × C57BL/6 hybrid	M/ F	d-Amphetamine sulfate	5 mg/kg	WT = HET for baseline locomotion; WT > HET for acute stimulation					
Gerber et al. (2001)	M1 (M1 muscarinic acetylcholine receptor)	WT, KO	C57BL/6 ES cells, injected into BALB/c blastocyst, then chimeras bred to C57BL/6	M	d-Amphetamine	1, 2, and 3 mg/ kg	KO > WT (3 mg/kg) for acute stimulation, WT = KO (1 and 2 mg/kg)					

Draski et al. (1994)	Hotfoot (ho; a spontaneously occurring single-gene mouse mutant that is a model of ataxia)	WT, ho/+ (phenotypically indistinguishable; combined as controls), ho/ho		M/F	d-Amphetamine	4 and 8 mg/kg	Control = ho/ho for baseline locomotion at age = 10 days and 30 days; Control > ho/ho for baseline locomotion at age = ˜168 days; control > ho/ho for acute stimulation at all doses (only 4 mg/kg tested in 10 and 30 days old; 4 and 8 mg/kg in adult)			Control = ho/ho for baseline wall climbing at age = 10 days; Control > ho/ho for baseline wall climbing at age = 30 days and ˜168 days; control > ho/ho for acute stimulation of climbing at all doses (only 4 mg/kg tested in 10 and 30 days old; 4 and 8 mg/kg in adult); Younger mice (40–70 days) exhibited a hyperthermic response-Control > ho/ho (4 mg/kg). Older mice (145–185 days) exhibited a hypothermic response-mutant > Control (4 mg/kg)
Jinnah et al. (1991)	HPRT (hypoxanthine-guanine phosphoribosyl-transferase)	WT, KO	129/Ola ES cells, 129/Ola × C57BL/6JLac × CBA/CaLac hybrid, ⩾N4 backcross to 129/J	M/F	d-Amphetamine sulfate	2, 4, 8, 16, and 32 mg/kg; each mouse received each dose once, 1 × per week	WT = KO for basline locomotion; KO > WT for acute stimulation to 8 mg/kg (only 2, 4, and 8 mg/kg tested for this trait)		WT = KO for baseline behavior rating (scale from sleeping to inactive to active to hyperactive to stereotypy to seizures); KO > WT for behavioral rating at 8 and 16 mg/kg only	
Jinnah et al. (1992)	HPRT (hypoxanthine-guanine phosphoribosyl-transferase)	WT, KO	129/Ola ES cells, 129/Ola × C57BL/6JLac × CBA/CaLac hybrid, ⩾ N6 backcross to C57BL/6J	M	d-Amphetamine sulfate	3, 6, 12, and 24 mg/kg; each mouse received each dose once, 1 × per week	WT = KO for baseline locomotion; KO > WT for acute stimulation to 3 mg/kg; at higher doses, peak stimulation was similar but there were shifts in the time-response curves			WT = KO for brain amphetamine levels

Table 9 (*continued*)

Citation	Gene	Geno	Background	Sex	Drug	Dose	Activity	Sensitization	CPP	Stereotypy	PPI	Other
Jinnah et al. (1992)	HPRT (hypoxanthine-guanine phosphoribosyl-transferase)	WT, KO	129/Ola ES cells, 129/Ola × C57BL/6JLac × CBA/CaLac hybrid, ⩾ N4 backcross to 129/J	M	d-Amphetamine sulfate	3, 6, 12, and 24 mg/kg; each mouse received each dose once, 1 × πper week	KO = WT (3 mg/kg; no stimulation); KO > WT for acute stimulation to 6 mg/kg; time-response curves appeared different (shifted or multi-phasic) between KO and WT for 12 and 24 mg/kg					WT = KO for brain amphetamine levels
Itier et al. (2003)	Parkin	WT, KO	129/Sv × C57BL/6 hybrid	M/F	Amphetamine	0.5, 1, and 5 mg/kg	KO < WT for baseline activity, KO < WT for acute stimulation (1 and 5 mg/kg)					
Kuteeva et al. (2005a)	GAL (galanin overexpression)	Non-TG, TG	C57BL/6 × CBA hybrid, N10 backcross to C57BL/6BKL	M	d-Amphetamine	3 mg/kg	Non-TG = TG for baseline locomotion, Non-TG > TG for acute stimulation					
Kuteeva et al. (2005b)	GAL (galanin overexpression)	Non-TG, TG	C57BL/6 × CBA hybrid, N10 backcross to C57BL/6BKL	M	d-Amphetamine	3 mg/kg	Non-TG ⩽ TG for baseline locomotion; Non-TG > TG for acute stimulation					
Shin et al. (2004)	tFGFR1 (tyrosine fibroblast growth factor receptor 1 underexpression TG)	Non-TG, TG	Not given	M/F	d-Amphetamine sulfate	2 mg/kg	TG > non-TG for baseline locomotion; TG = non-TG for acute stimulation					
Bronsert et al. (2001)	5-HT_{1B} (serotonin 1B receptor)	WT, KO	129/SvPas × 129/Sv-ter hybrid, N6 backcross to 129/SvEvTac	M	d-Amphetamine sulfate	4 injections at 15-min intervals, repeated at 2-d intervals, × 4-cumulative dose each day: 0.5, 1, and 2 and 4 mg/kg (i.p.) or 0.6, 1.2, 1.8, and 2.4 mg/kg (i.v.) to examine acute stimulation;	KO = WT for baseline locomotion; KO > WT for dose-dependent acute stimulation (i.p. only; pattern similar for i.v., but not significant)	KO > WT for development of sensitization (i.v., but not i.p.)				KO > WT for amphetamine-increased rearing (i.v. only, no effect of i.p. amphetamine on rearing)
Scearce-Levie et al. (1999a)	5-HT_{1B} (serotonin 1B receptor)	WT, KO	129/SvPas × 129/Sv-ter × 129/SvEvTac hybrid	NS	Amphetamine	1.5 and 6 mg/kg	WT = KO for baseline locomotion; KO > WT for acute stimulation					

Bengel et al. (1998)	5-HTT (serotonin transporter)	WT, HET, KO	129/Sv R1 ES cells, 129/Sv × C57BL/6J × CD-1 hybrid and 129/Sv × C57BL/6J hybrid	F	(+)Amphetamine hydrochloride	5 mg/kg	WT = HET = KO for baseline locomotion; WT = HET = KO for acute stimulation				
Nakajima et al. (2004)	TNF-α (tumor necrosis factor α)	WT, KO	TT2 ES cells, C57BL/6 × CBA/JNCrj hybrid, N8 backcross to C57BL/6	M	Methamphetamine hydrochloride	1 mg/kg (× 8, once per day) for sensitization development, then 1 mg/kg for expression of sensitization after 8 days off drug; 1 and 4 mg/kg (× 3, every other day) for CPP	KO < WT for baseline locomotion, but KO = WT after habituation; WT = KO for acute stimulation	KO > WT for development and expression of sensitization	KO > WT (at 1, but not 4 mg/kg)		
Ventura et al. (2004)	Fmr1 (fragile × mental retardation gene)	WT, KO	129/OlaHsd ES cells, 129/OlaHsd × C57BL/6 × FVB/N hybrid	M	d-Amphetamine sulfate	2 mg/kg	KO > WT for baseline locomotion; WT > KO for acute stimulation				WT > KO at baseline for novel object recognition; amphetamine impaired recognition in WT, and improved recognition in KO
Hess et al. (1996)	Cm (coloboma mutant)	HET, WT	Mutation identified on C3H/HeH × 101/H F1, then N32 backcross to C57BL/6By, then N10 backcross to C3H/HeSnJ	M/F	d-Amphetamine sulfate	2, 4, 8, and 16 mg/kg (× 1 for each dose tested, with 7 days between doses)	HET > WT for locomotion after saline, d-amphetamine suppressed high baseline of HET, little response in WT mice			*Cm*/+ = WT	
Hess et al. (1996)	Sp (Mini-Snap overexpression TG) + Cm (coloboma mutant)	Sp/Sp +/+, Sp/Sp Cm/+	Coloboma: mutation identified on C3H/HeH × 101/H F1, then N32 backcross to C57BL/6By, then N10 backcross to C3H/HeSnJ Mini-*Snap*: C3H/HeJ × C57BL/6 hybrid	NS	d-Amphetamine sulfate	4 mg/kg	SNAP over-expression normalized *Cm*/+ mutant hyperactivity and normalized acute stimulant response; Sp/Sp +/+ = Sp/Sp Cm/+ for both traits				

See Table 2 for legend.

may normally confer sensitivity to the rewarding effects of stimuli associated with amphetamine. However, in a population of human methamphetamine addicts and controls, no association was found between polymorphisms in the CART gene and the likelihood of methamphetamine dependence (Morio et al., 2006), suggesting that naturally occurring CART gene polymorphisms may not be important to the clinical syndrome.

The DAT and each of the dopamine D_1, D_{1A}, D_2, D_3, and D_4 receptors have been examined for their roles in amphetamine responses using KO mice. Some data support an association of number of repeat alleles of the DAT gene with risk for methamphetamine psychosis (Ujike et al., 2003). Further, DAT density, quantified using positron emission tomography, was decreased in methamphetamine users compared to non-users (Sekine et al., 2003). These data cannot differentiate between a pre-existing versus a methamphetamine-induced reduction in DAT levels. However, DAT KO mice displayed amphetamine-conditioned place preference sooner and the preference lasted longer than in WT mice (Budygin et al., 2004), suggesting that the absence of DAT throughout development enhanced conditioned reinforcement. In multiple studies examining the acute locomotor response to amphetamine of DAT KO and WT mice, the markedly elevated baseline locomotion of the KO mice likely impacted their ability to exhibit a locomotor stimulant response. In fact, WT mice exhibited the typical activation, whereas KO mice showed locomotor depression (Gainetdinov et al., 1999; Giros et al., 1996; Spielewoy et al., 2001; Zhuang et al., 2001). The ability of stimulants to reduce the hyperactivity of DAT KO mice has suggested to some that these mice may serve as a model of attention deficit hyperactivity disorder (ADHD).

Results for amphetamine-related responses in dopamine receptor KO mice have been somewhat more variable or subject to the idiosyncrasies of specific experimental designs; the reader is encouraged to examine Table 2. One trait that has been examined in several of these and other dopamine-related mutants is PPI of the startle reflex and disruption of the reflex by amphetamines. PPI of the startle reflex was developed as an animal behavioral model of sensorimotor gating deficits. This animal model is thought to be relevant to several mental illnesses for which sensorimotor gating is affected, including schizophrenia (Braff et al., 1995). Chronic amphetamine use can lead to schizophrenia-like symptoms that appear to follow a time course related to duration of use, progressing from a non-psychotic to a prepsychotic state and ultimately to a severely psychotic state (Ujike and Sato, 2004). Measurement of PPI in single-gene mutant mice has been used to identify neurobiological mechanisms associated with disruptions in sensorimotor gating, although the concentration has been on acute amphetamine effects, rather than chronic. Thus, in dopamine D1, D3, and D4 receptor KO mice, disruption of PPI by amphetamine was intact, whereas amphetamine did not disrupt PPI in D2 receptor KO mice (Ralph et al., 1999; Ralph-Williams et al., 2002). In mice with deletion of only the long isoform of the D2 receptor, disruption of PPI by amphetamine was intact (Xu et al., 2002), suggesting that the short isoform alone could mediate this effect of amphetamine on PPI. An additional study suggests that the signaling pathway requiring DARPP-32 is also critical in mediating amphetamine-induced disruption of PPI (Svenningsson et al., 2003). One modulator of this protein is dopaminergic neurotransmission.

The body of work examining amphetamine reward-related traits in mice with dopamine-related genetic alterations is small. At the time of our literature review, we found only five studies examining conditioned rewarding effects, and none examining self-administration. There was one study showing a deficit in brain stimulation reward in D_2 receptor KO mice (Elmer et al., 2005). Given the large literature supporting dopamine involvement in the neural circuitry thought to mediate amphetamine reward, more research in this area seems warranted.

9. Glutamate- and glycine-related genes: amphetamine and methamphetamine (Table 3)

Glutamatergic neurons in the prefrontal cortex provide excitatory input to dopamine neurons in the nucleus accumbens and ventral tegmental area, thought to be involved in drug reward. Glutamate systems have been shown to function in both synaptic plasticity and conditioned behaviors, and several lines of evidence suggest that they may also play an important role in drug-associated learning and addiction (Jones and Bonci, 2005). Pharmacological studies have shown that glutamate receptor antagonists impair the development of place preference for amphetamine (Jackson et al., 2000). In addition, NMDA-type glutamate receptor antagonists blocked the development of behavioral sensitization to amphetamine, while AMPA-type glutamate receptor antagonists impaired the maintenance of sensitization and decreased conditioned responding for amphetamine self-administration (Jackson et al., 2000). Glutamate levels increased in response to amphetamine exposure (Del Arco et al., 1999), and pretreatment with metabotropic glutamate receptor antagonists decreased the levels of extracellular dopamine released in response to methamphetamine (Golembiowska et al., 2003).

Results from gene targeting experiments have extended these results and confirmed that glutamate systems are relevant to amphetamine-related behaviors (Table 3). However, with the exception of one study that examined amphetamine-induced conditioned place preference in GluRε1 (aka NR2A) KO mice, the focus has been largely on sensitivity and neuroadaptation. Deletion of GluRε1 caused a reduction of locomotor stimulation in response to acute methamphetamine, as well as a lower magnitude of sensitization to repeated methamphetamine exposure (Miyamoto et al., 2004b). Mice carrying a hypomorphic allele of NR1 (the receptor subunit common to all

NMDA-type heteromers) also exhibited decreased locomotion relative to WT mice in response to acute amphetamine, but interpretation of this result may be complicated by the increased stereotypy of this strain (Miyamoto et al., 2004a). Further, a mutant with an NR1 NMDA receptor subunit with reduced function that was expressed only in dopamine D1 receptor-containing cells, did not exhibit an alteration in amphetamine response (Heusner and Palmiter, 2005). Deletion of the metabotropic GluR1 receptor subunit caused an increase of behavioral responses to amphetamine at higher doses, such that the KO mice exhibited less normal locomotion and more stereotypy and seizures than the WT (Mao et al., 2001). The locomotor response to amphetamines of GluR2 KO mice has not been reported, but this mutant was impaired in certain aspects of stimulus–reward learning, and failed to increase conditioned responding after methamphetamine administration (Mead and Stephens, 2003).

Homer proteins are important modulators of glutamate signaling and interact with both NMDA and AMPA receptors. Deletion of either Homer-1 or -2 caused a decrease in basal extracellular glutamate levels in the nucleus accumbens, whereas Homer-1 mutants also exhibited increased glutamate content in the prefrontal cortex (Szumlinski et al., 2004). In addition, both of these mutants were more sensitive to the stimulatory effects of acute methamphetamine (Szumlinski et al., 2005). Another important regulator of glutamatergic signaling is glycine, which must bind to the strychnine-insensitive glycine modulatory site in the process of NMDA receptor activation. Deletion of the GlyT1 glycine transporter caused increased concentrations of glycine at the synapse, and thus an increased ratio of NMDA/AMPA signaling. Animals heterozygous for the GlyT1 deletion showed WT levels of stimulation in response to amphetamine administration, but did not display the normal disruption of PPI exhibited by WT animals (Tsai et al., 2004). This suggests yet another target for consideration in the search for the precise substrates involved in the effects of amphetamines on PPI. Recent findings also support deficits in glutamate transmission in schizophrenia, a condition associated with deficits in sensorimotor gating (Hahn et al., 2006).

10. Noradrenergic-related genes: amphetamine and methamphetamine (Table 4)

The locus coeruleus is a noradrenergic nucleus that projects to regions including the nucleus accumbens, ventral tegmental area, and prefrontal cortex. Psychostimulant administration has been associated with increased norepinephrine (NE) levels in the prefrontal cortex (Florin et al., 1994). In addition, lesions of the locus coeruleus cause a reduction in amphetamine-induced hyperactivity (Mohammed et al., 1986), indicating that noradrenergic signaling is involved in this behavioral response. Mice which are deficient in NE from birth (dopamine β-hydroxylase KO mice) are more sensitive to the locomotor effects of a single dose of amphetamine, but exhibit a reduction in sensitization to the drug over repeated doses (Weinshenker et al., 2002). Mice lacking the NE transporter also have increased sensitivity to acute amphetamine (Xu et al., 2000a).

The adrenergic receptor gene family is diverse, and although these proteins were originally defined pharmacologically (for review see Calzada and De Artinano, 2001), a detailed characterization of the functions of various receptor subtypes has been difficult due to a lack of highly selective antagonist compounds. α_1-adrenoceptors (AR) are coupled to G_q and signal via phospholipase C and inositol triphosphate pathways (Koshimizu et al., 2003). α_1-AR activity is considered important for motor activity, arousal, and exploratory behaviors (Stone et al., 1999), and the α_1-AR antagonist prazosin reduces amphetamine-induced hyperactivity (Blanc et al., 1994). In contrast, α_2-ARs couple to G_i/G_o (Kurose et al., 1991), which inhibits the production of cAMP by adenylyl cyclase, and inhibits NE release and firing of noradrenergic neurons (Starke, 2001). KO mice deficient in specific AR subtypes have contributed to our understanding of the role that noradrenergic signaling plays in amphetamine-related behaviors. Consistent with an excitatory role for α_1-ARs, knockout of either α_{1B}-AR or α_{1D}-AR resulted in reduced locomotor stimulation in response to an acute dose of amphetamine (Auclair et al., 2002, 2004; Drouin et al., 2002; Sadalge et al., 2003). Further, α_{1B}-AR KO mice were impaired for behavioral sensitization to repeated amphetamine or methamphetamine administration, compared to their WT counterparts (Auclair et al., 2004; Battaglia et al., 2003; Drouin et al., 2002). Mice lacking the α_{2A}-AR exhibited a phenotype similar to that of the NE-deficient dopamine β-hydroxylase KO mice. They showed an increase in acute stimulation and decreased development of behavioral sensitization to amphetamine (Juhila et al., 2005). The role of α_{2C}-AR is less clear, since male, but not female, KO mice exhibited increased sensitivity to acute amphetamine, but this result is still consistent with an inhibitory role for α_2-ARs (Sallinen et al., 1998). Future work using these subtype-specific KO strains will hopefully provide more information on the behavioral functions of this complex receptor family.

11. Cell support and signaling proteins: amphetamine and methamphetamine (Table 5)

Signaling cascades that contribute to addiction, and that protect or delay the development of addiction, have been nicely reviewed by Ron and Jurd (2005), with a specific focus on cocaine and ethanol. Some of the same molecular events are likely to be involved in amphetamine-mediated behaviors. A small number of studies with single-gene mutants have involved cell signaling-related proteins. Details can be found in Table 5.

Obvious candidates to examine for involvement in the effects of amphetamines are those that mediate coupling of

dopamine receptors to adenylyl cyclase. The GTP-binding protein $G\alpha_{olf}$ subunit is the predominant form in the striatum that is involved in dopamine D1 and adenosine A_{2A} receptor signaling. Mice possessing a single copy of a null mutant allele for the gene that expresses $G\alpha_{olf}$ exhibited both reduced baseline and amphetamine-stimulated behavior, compared to WT controls (Herve et al., 2001). In mice lacking G protein-coupled receptor kinase 6, which mediates desensitization of dopamine receptors, increased sensitivity to the locomotor stimulant effects of amphetamine was seen (Gainetdinov et al., 2003). The enhanced coupling of D2-like dopamine receptors to striatal G proteins seen in these mice could have played a role in this increased stimulant response. Phosphodiesterase 1B KO mice also exhibited an enhanced locomotor response to methamphetamine (Reed et al., 2002). This calcium/calmodulin-dependent phosphodiesterase is highly expressed in the striatum, as well as in other regions with high levels of dopaminergic innervation. Striatal slices from these mice were used to demonstrate increased sensitivity to dopamine D1 receptor activation, as indicated by increased levels of DARPP-32 and other transduction-related molecules (Reed et al., 2002). Thus, phosphodiesterase 1B appears to play a significant role in dopaminergic functioning, and its absence resulted in enhanced dopamine receptor signaling. Another signaling pathway relevant to the effects of amphetamine involves the dopamine D2 receptor and the Akt/glycogen synthase kinase 3 (GSK-3) signaling cascade. Mice heterozygous for a null mutation of the GSK-3β gene exhibited a blunted response to amphetamine. The set of studies reviewed in this paragraph support both dopamine D1 and D2 receptor signaling in locomotor stimulation to amphetamines. Some differences in locomotor response to amphetamine have also been seen in D1 and D2 receptor KO mice (see Table 2).

Behavioral sensitization induced by repeated psychostimulant administration is thought to involve specific changes in dopaminergic pathways. The R11 β-protein kinase A (PKA) isoform is highly expressed in mouse stratium and serves a role in dopamine receptor signaling. R11β-PKA mutant mice did not differ in acute locomotor response to amphetamine; however, they exhibited a larger magnitude of behavioral sensitization (Brandon et al., 1998). This suggests a role for this PKA isoform in behavioral neuroadaptation to amphetamine.

Cell support and signaling proteins, involved in neural development, neuroprotection, and survival, have also been examined for their roles in amphetamine-related behaviors using null mutant mice. Mice heterozygous for a mutant brain-derived neurotrophic factor (BDNF) allele exhibited increased sensitivity to the stimulant effects of amphetamine (Dluzen et al., 2001; Pineda et al., 2005). These mice were also found to have increased striatal dopamine levels in the absence of amphetamine treatment; the effect of acute amphetamine on striatal dopamine concentrations was not examined in these mice (Dluzen et al., 2001). When the BDNF KO was combined with the expression of the Huntington gene (htt), these mice showed an exacerbation of the insensitivity to amphetamine seen in the HTT transgenic. These data suggest that the decreased BDNF expression that has been observed in Huntington's disease patients may contribute to exacerbation of dopamine-related motor disturbances characteristic of this disease (Pineda et al., 2005). Finally, glial-derived neurotrophic factor overexpression transgenic mice exhibited enhanced sensitivity to amphetamine-induced locomotor stimulation (Kholodilov et al., 2004). This may have been related to the increased number of ventral tegmental area neurons surviving into adulthood in these mice.

In general, additional research is needed to define which of these signaling and cell support molecules might be involved in more complex amphetamine reward-related traits. In addition, extension of the information on the effects of these mutations on brain circuitry underlying amphetamine sensitivity, neuroadaptation, and reward would be particularly useful as the research community attempts to move toward a more comprehensive approach to genetic investigations (e.g., examining combined genetic effects and interactions), from a one-gene-at-a-time approach.

12. Steroids and other peptides: amphetamine and methamphetamine (Table 6)

Amphetamine-related research involving single-gene knockout or overexpression mutants for a diverse set of steroid- and other peptide-related genes is summarized in Table 6. This research area has not been extensive, and whether significant expansion is warranted will depend upon the significance of the initial results, and whether evidence from other approaches suggests the involvement of specific peptides in amphetamine-related traits. The cholecystokinin receptor 2 (CCK_2) and one of its associated ligands have been studied. Ventral tegmental area dopamine cells have been shown to express cholecystokinin (Hokfelt et al., 1980), and cholecystokinin enhances dopamine-induced locomotor activity (Crawley, 1992). Pretreatment with the CCK_2 receptor antagonist, L-365,260 was shown to have no effect on amphetamine-induced locomotor stimulation in one study (Vasar et al., 1991), but enhanced the magnitude of this amphetamine effect in another (Alttoa and Harro, 2004). Results from studies using KO mice were dose-dependent and present somewhat complicated results with regard to interpretation. Mice lacking functional CCK_2 receptors were less stimulated by 3 mg/kg amphetamine compared to WT mice, but more stimulated by 6 mg/kg amphetamine; a 1 mg/kg dose did not induce stimulation in either genotype (Koks et al., 2001, 2003; Runkorg et al., 2006). L-365,260 has been shown to alter the development of behavioral sensitization to amphetamine; low doses increased sensitization while higher doses attenuated amphetamine-induced locomotor sensitization (Wunderlich et al., 2000). CCK_2 receptor KO mice showed an enhanced magnitude of

amphetamine-induced locomotor sensitization compared to WT mice (Runkorg et al., 2006). These results would seem to agree most closely with the results using lower doses of L-365,260. Perhaps the specificity of the antagonist for the CCK_2 receptor is reduced at higher doses. Previous research has shown that infusion of cholecystokinin into the ventral tegmental area, which would presumably activate CCK_2 receptors, can enhance amphetamine-induced conditioned place preference (Pettit and Mueller, 1989). Consistent with these findings, WT mice show enhanced amphetamine-conditioned place preference compared to mice lacking CCK_2 receptors (Runkorg et al., 2006). Gastrin also binds to CCK_2 receptors with agonist properties, and this peptide has been implicated in some amphetamine-related behaviors. Mutant mice lacking gastrin were less affected by amphetamine-induced disruption of PPI compared to WT mice (van den Buuse et al., 2005b).

13. Methylphenidate (Table 7)

ADHD is a psychiatric disorder that is diagnosed when patients present with hyperactivity (particularly motor hyperactivity), attention deficits, and impulsive behavior that supersedes normal daily functioning (Himelstein et al., 2000). For over 50 years, this disorder has been treated with amphetamines, including methylphenidate (Swanson et al., 1998). These drugs improve attention and decrease motor hyperactivity. Since methylphenidate is widely prescribed for this disorder, much of the research performed to understand the genetic basis of the behaviors caused by this drug has focused on alleviating ADHD-like symptoms. Results from studies examining the behavioral response to methylphenidate in genetically engineered mice are summarized in Table 7.

Methylphenidate acts as an indirect dopamine agonist, having effects on the DAT. A number of studies have examined the role of naturally occurring DAT variants in the clinical response to methylphenidate, but results from these studies are not entirely consistent. While some studies show no difference in response to methylphenidate among groups of individuals with different DAT polymorphisms (Mick et al., 2006; van der Meulen et al., 2005; Zeni et al., 2007), other studies have shown an association between a DAT polymorphism and the response to methylphenidate, but not always in the same direction (Cheon et al., 2005; Kirley et al., 2003; Roman et al., 2002; Winsberg and Comings, 1999). The DAT KO mouse has been examined for a number of behaviors. Mice lacking the DAT exhibit greater baseline locomotion than WT mice. When the mice were treated with methylphenidate they displayed a paradoxical response; WT mice showed the predicted stimulation after methylphenidate treatment, whereas mice lacking the DAT showed locomotor depression (Gainetdinov et al., 1999). A similar paradoxical effect was observed when these mice were tested for PPI. Mice lacking the DAT displayed a reduced baseline PPI compared to WT mice. Methylphenidate (60 mg/kg) enhanced PPI in the DAT KO mice, but reduced this response in WT mice (Yamashita et al., 2006). These data are consistent with motor symptoms in ADHD individuals. Therefore, the DAT KO mouse appears to model the motor aspects of this disorder, as well as the attentional aspects, given their reduced baseline PPI. In contrast, when tested for methylphenidate-induced conditioned place preference, mice of the two genotypes were equally sensitive (Sora et al., 1998).

ADHD co-occurs with generalized thyroid hormone resistance; 50–70% of patients with this thyroid condition meet the criteria for ADHD (Hauser et al., 1993). Generalized thyroid hormone resistance is caused by a mutation in the human thyroid receptor-β gene, and is characterized by elevated levels of thyroid hormones in serum (Mixson et al., 1992; Takeda et al., 1992). Because of the association between generalized thyroid hormone resistance and ADHD in the literature, mice carrying alterations in the thyroid receptor-β gene have been studied as a possible model of ADHD. Male knock-in mice carrying a mutated thyroid receptor-β allele from a patient who was diagnosed with both generalized thyroid hormone resistance and ADHD were less impaired by methylphenidate on a vigilance task compared to heterozygous or WT mice. Female mice were equally sensitive to this effect, regardless of genotype (Siesser et al., 2005). The same mutated allele was used to create a pituitary-specific transgenic mouse. When this transgenic mouse was tested, there were no observable differences in baseline locomotor activity, but male WT mice were more stimulated by methylphenidate compared to transgenic mice. Female transgenic and WT mice were equally sensitive (Siesser et al., 2006). These data provide support for the involvement of the thyroid receptor-β in methylphenidate behaviors. Further work will be needed to fully dissect this relationship.

14. MDMA (Table 8)

Most of the studies on MDMA using KO models have focused on the serotonin and dopamine systems, consistent with the known mechanism of action of MDMA. The serotonin system has been implicated in MDMA-induced locomotor activity. In rats, pretreatment with serotonin uptake inhibitors attenuated MDMA-induced locomotion (Callaway et al., 1990). Similarly, in humans, pretreatment with the uptake inhibitor, fluoxetine, attenuated many of the subjective effects of MDMA, including elation, positive mood, arousal, and feeling high and stimulated (Tancer and Johanson, 2007). These data are consistent with results from KO mice lacking the serotonin transporter gene. Mice lacking this gene were less stimulated by MDMA than were WT mice (Bengel et al., 1998).

The serotonin 1B subtype receptor in particular has been implicated in a number of MDMA-induced behaviors. This receptor can function as both an autoreceptor on serotonin neurons and as a postsynaptic receptor. The lack of specific

agonists and antagonists for this receptor make the null mutant the best approach for examining its role. Compared to serotonin 1B KO mice, WT mice were more stimulated by MDMA; however, mice of these genotypes did not differ in sensitivity to the depressant effects of MDMA on rearing behavior or nose pokes (Scearce-Levie et al., 1999a, b). In contrast, the mutant mice were more sensitive to the stereotypic effect of MDMA compared to WT mice (Scearce-Levie et al., 1999a). The serotonin 1B receptor has also been shown to be involved in the effect of MDMA on PPI. There were no baseline differences in magnitude of startle or PPI; however, mice lacking serotonin 1B receptors were less sensitive to the depressant effect of MDMA on startle magnitude compared to WT mice, and they exhibited greater sensitivity to the increase in PPI associated with MDMA treatment (Dulawa et al., 2000). These data were interpreted as indicating that serotonin-induced activation of serotonin 1B receptors disrupts PPI.

Pharmacological studies have implicated dopamine receptors in MDMA-induced locomotor stimulation. Haloperidol (a dopamine receptor antagonist with highest affinity for D_2-like receptors), eticlopride (a D_2 antagonist), and SCH-23390 (a D_1 antagonist), have all been shown to attenuate MDMA-induced locomotor stimulation (Ball et al., 2003; Bubar et al., 2004; Kehne et al., 1996). In some, but not all, cases, data from mice carrying null mutations of one of the dopamine receptors have provided similar results. Consistent with the results of pharmacology studies, mice lacking D_2 or D_3 receptors were less sensitive to MDMA-induced stimulation compared to WT mice; some of these results were sex-specific. However, mice lacking the D_{1A} receptor were more stimulated by MDMA, a result that is contrary to the pharmacological antagonist result (Risbrough et al., 2006).

15. Discussion

Inbred strain studies and selective breeding projects have confirmed that genetic variation influences relative sensitivity and neuroadaptation to amphetamine-like drugs, as reflected by behavioral trait measurements. Further, genetic correlations identified in selected lines have suggested some common genetic influences for different amphetamine effects and for some effects of amphetamine compared to those of other abused drugs. These data suggest that common neurobiological mechanisms can also be identified. Comparison of inbred strain behavioral and neurobiological variation is one approach that can provide convincing evidence for a particular mechanism, when very large inbred strain panels are used; the more common two to four strain comparisons will not provide a rigorous test of such relationships. Large strain panels have not often been used in psychostimulant drug research, although the work of Janowsky et al. (2001), which examined DAT density in a panel of RI strains and correlated this with multiple behavioral traits, serves as one example. As genome-wide sequence information for multiple inbred strains has increased, more direct genotype–phenotype, *in silico* mapping approaches (e.g., Grupe et al., 2001) are becoming feasible. Gene and gene expression co-mapping in selected lines (e.g., Palmer et al., 2005) also represents a more direct path to gene finding for complex, drug-related traits.

As is apparent from the multiple tables in this review, many investigators have used mice with single-gene manipulations to get at mechanisms associated with the behavioral effects of amphetamine-like drugs. Some of the mechanisms which had been previously identified using other techniques, such as pharmacological antagonism, were confirmed by analyses involving single-gene mutant mice. However, some data arising from the use of such mice have suggested new targets for investigation as well. For example, not discussed above, but included in Table 9, are the results from investigations of the role of the trace amine 1 receptor (TA1) in amphetamine sensitivity (Wolinsky et al., 2007). Trace amines can be synthesized from more abundant amines, such as phenylalanine or tyrosine, and are found in low concentrations in the brain. They have been suggested to play a role in some neuropsychiatric disorders, and amphetamines are potent agonists at TA1 receptors (Bunzow et al., 2001; Wolinsky et al., 2007). TA1 KO mice showed altered sensitivity to the effects of amphetamine on locomotor behavior. Because this receptor is found in high concentrations in the amygdala and other limbic regions that are part of the drug reward circuitry (Borowsky et al., 2001; Bunzow et al., 2001), it is an exciting target for additional study into its influence on amphetamine-related traits.

There are relatively few cases where a single-gene mutant has been examined for the same behavioral response to more than one amphetamine-like drug. One case where this has occurred is with the serotonin 1B receptor mutant. Mice lacking this gene are more sensitive to the locomotor stimulant effects of methylphenidate (Scearce-Levie et al., 1999a) and amphetamine (Scearce-Levie et al., 1999a; Bronsert et al., 2001) than WT mice, but are less sensitive than WT mice to the stimulant effects of MDMA (Scearce-Levie et al., 1999a, b). This is interesting because MDMA is more potent at inhibiting the serotonin transporter than the other amphetamines. DAT knockout mice have also been tested for their acute stimulant response to these three drugs. In general WT mice are stimulated by an acute injection of methylphenidate, MDMA, and amphetamine while KO mice are depressed by an acute injection of these drugs (Gainetdinov et al., 1999; Powell et al., 2004; Spielewoy et al., 2001; Zhuang et al., 2001; but see Giros et al., 1996). Therefore, for this trait, DAT KO had similar consequences across the three drugs. Finally, mu opioid receptor KO and WT mice have been tested for susceptibility to conditioned place preference induced by amphetamine (Marquez et al., 2007) and MDMA (Robledo et al., 2004). Sensitivity of the WT and KO mice was equivalent for both drugs. An approach that examines the role of a particular gene for systematically measured traits, using

equipotent drug doses, may provide important insights about differences in actions of these structurally related drugs for specific phenotypes.

It has been pointed out many times that one advantage of the single-gene mutation approach is specificity that may not exist with pharmacological antagonism. However, as we have argued previously, complete deletion of a major receptor or other critical protein could require massive developmental compensation for viability (Crabbe et al., 2006). Thus, results may not be the same for an animal that has never possessed a given protein as for one in which the protein function is blocked or attenuated in adulthood. Development of conditional knockout and rescue methods offer the promise of better interpretability, but have not yet found wide usage (Choi et al., 2002; Gaveriaux-Ruff and Kieffer, 2007). On the other hand, identification and study of the specific compensations occurring as a result of gene deletion can provide insight into the potential for functional redundancy in the developing nervous system.

Some investigators have included heterozygous KO mice in their investigations. Sometimes this is for the practical reason that mice that are homozygous for a particular mutant allele are not viable. However, even when the homozygous KO is fully viable, this practice could serve to assuage concerns related to developmental compensations. An effect of a mutant allele may be seen in a heterozygous KO mouse in the absence of the more extreme developmental compensations that may occur in the homozygous KO. Further, it has been argued that because human disorders are more likely to be associated with genetic alterations resulting in reduced function, rather than complete loss of function, heterozygous mutants may be a more relevant study population (Kalueff et al., 2007). The combined information gained from studying all three genotypes could add important insights into the influence of the mutant allele on the trait in question.

Gene mapping and expression analyses are beginning to identify specific genomic regions where genetic variation influences amphetamine-related responses. The ultimate goal of this research is to identify the specific genes that are involved and then determine their precise role in a given behavior. Due to the complexity of drug-related traits and their likely multigenic determination, this is a difficult, but not intractable, goal. However, gene mapping and expression analyses ask a somewhat different question than analyses with mutant animals. With the exception of overexpression transgenics and rare knockdown mutants, single-gene mutants are engineered to possess a complete gene deletion. Thus, no functional protein is produced (however, see discussion of the use of heterozygote knockouts above). Gene mapping and expression analyses take advantage of existing polymorphisms which may represent differences in sequence that predict conformational changes in the protein. Thus, in at least some cases, more than one version of a protein may exist in a given population, with differing functional characteristics. Some sequence differences may result in altered gene expression. This relative difference in function or expression is likely to be markedly different than absent function and may be more representative of population-based genetic variation. However, there are also naturally occurring disease-related gene deletions that can be validly modeled in deletion mutants.

QTL analysis can be validly defined as a non-hypothesis-driven fishing expedition, unless one is satisfied with the general hypothesis that there are genes in specific regions of the genome that influence the behavioral trait under study. However, with the technological developments that have been seen in the past two decades, making genome-wide analysis more efficient and less costly, this approach can now be seen as a reasonable tool for hypothesis generation. Further, there are now many internet resources that allow more sophisticated genetic hypothesis generation. Trait × genotype correlations may point to specific genes that should be examined for drug-related responses. Utilization of this information provides a more thoughtful approach to identifying genes for examination than restricting research to the obvious candidates based on pharmacology and circuitry. However, we should not lose sight of environmental factors, which may act additively with genetic effects or interact with specific genes, in the determination of complex addiction-related traits. Even a simple factor like rearing from birth in all-male, all-female, or mixed-sex litters has been shown to influence an amphetamine response (Cirulli et al., 1997). Further, the direction of effect of a stressor on the balance of dopamine systems can be influenced by past individual experiences (Cabib et al., 2002). One might suspect that these factors would additionally interact with genetic differences in the determination of drug responses. In fact, Cabib et al. (2000) showed that strain differences in place conditioning and locomotor response to amphetamine were strongly affected by a forced period of food shortage. More work is needed that examines gene × environment interactions important in amphetamine addiction.

In conclusion, at this time there is a large literature on responsiveness to amphetamines in single-gene mutant mice, and considerably less information from more direct genetic approaches such as gene mapping, gene expression, or viral-mediated gene transfer. QTL mapping has identified genetic regions of interest and even some promising candidate genes. However, as we have argued previously, proof of a QTG will require the careful assembly of evidence from multiple sources (Belknap et al., 2001). To date, the largest body of literature on the genetics associated with amphetamine-related behavioral effects has focused on locomotor responses. There is a smattering of reports examining conditioned place preference, but scarce literature as yet examined the genetics of other reward-related traits such as self-administration, nor is there a literature on aversive effects other than stereotypy. There is also a need for genetic investigations into susceptibility to relapse/reinstatement. Yan et al. (2006) have shown that such investigations are

not intractable in mice. We did not search the literature for studies examining differential genetic sensitivity to amphetamine-induced neurotoxicity that did not also measure behavior, but this would be another important area to pursue. In general, there is a great deal of work to be done in the quest for genes that influence the development and acceleration of amphetamine use, dependence, withdrawal, relapse, and toxicity.

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