Table 2. Cocaine responses in monoamine receptor transgenic mice

Citation	Gene	Micro-dialysis	Loco-motion	Sensiti-zation	CPP	Self-administration	PPI	Adverse effects
Xu, M. *et al.* 1994	D_1 KO		Decreased					
Miner, L.L. *et al.* 1995	D_1 KO				Unaffected			
Xu, M. *et al.* 2000	D_1 KO		Eliminated					
Caine, S.B. *et al.* 2007	D_1 KO					Eliminated		
Karlsson, R.M. *et al.* 2008	D_1 KO			Eliminated				
Doherty, J.M. *et al.* 2008	D_1 KO						Eliminated cocaine-induced impairments	
Chausmer, A.L. *et al.* 2002	D_2 KO		Unaffected					
Rouge-Pont, F. *et al.* 2002	D_2 KO	Increased DA release						
Caine, S.B. *et al.* 2002	D_2 KO					Increased		
Welter, M. *et al.* 2007	D_2 KO		Decreased		Slight reduction			
Doherty, J.M. *et al.* 2008	D_2 KO						Partially eliminated cocaine-induced impairments	
Xu, M. *et al.* 1997	D_3 KO		Increased		Increased			
Carta, A.R., C.R. Gerfen & H. Steiner. 2000	D_3 KO		Decreased	Eliminated				
Katz, J.L. *et al.* 2003; Rubinstein, M. *et al.* 1997	D_4 KO		Increased					
Elliot, E.E., D.R. Sibley & J.L. Katz. 2003	D_5 KO		Decreased					
Karlsson, R.M. *et al.* 2008	D_5 KO		Unaffected	Decreased	Unaffected			
Doherty, J.M. *et al.* 2008	D_3 KO						Increased cocaine-induced impairments	

Continued.

Table 2. *Continued*

Citation	Gene	Micro-dialysis	Loco-motion	Sensiti-zation	CPP	Self-administration	PPI	Adverse effects
Karasinska, J.M. *et al.* 2005	D_1/D_3 KO		Decreased		Decreased			
Rocha, B.A. *et al.* 1997	$5\text{-}HT_{1B}$ KO					Increased		
Belzung, C. *et al.* 2000	$5\text{-}HT_{1B}$ KO				Unaffected			
Shippenberg, T.S., R. Hen & M. He. 2000	$5\text{-}HT_{1B}$ KO	Increased DA release				Increased		
Salomon, L. *et al.* 2007	$5\text{-}HT_{2A}$ KO		Increased	Unaffected				
Rocha, B.A. *et al.* 2002	$5\text{-}HT_{2C}$ KO							
Allan, A.M. *et al.* 2001	$5\text{-}HT_3$ over-expression				Decreased			
Witkin, J.M. *et al.* 2007	$5\text{-}HT_7$ KO							Increased cocaine-induced seizures and lethality
Schank, J.R. *et al.* 2006	DBH KO		Increased		Preference at 5 mg/kg, aversion at 20 mg/kg			
Jasmin, L., M. Narasaiah & D. Tien. 2006	DBH KO				Eliminated			
Gaval-Cruz, M. *et al.* 2008	DBH KO							No effect on cocaine induced seizures
Drouin, C. *et al.* 2002	α_{1b} KO		Decreased	Decreased				

on a combination of monoaminergic effects or in the absence of DAT other monoaminergic mechanisms can compensate for the absence of DAT. Again, like the circumstance with cocaine, this is not to say that DA has no role, even without DAT. Systemic AMPH still increases extracellular DA in the nucleus accumbens without DAT,[21,64] although local striatal infusion does not.[64] Furthermore, this study also demonstrated that AMPH would reduce DA cell firing in WT mice but not in DAT KO mice. This effect is probably due to reduced autoreceptor function in DAT KO mice,[65] which reveals an underlying non–DAT-mediated stimulatory effect that can be observed when autoreceptor feedback is impaired.[66] With these data, as well as the data discussed earlier for cocaine, it would seem likely that serotonergic mechanisms are involved in AMPH CPP in DAT KO mice. Consistent with this hypothesis, AMPH-induced CPP was abolished by pretreatment with a $5\text{-}HT_{1A}$ receptor antagonist in DAT KO mice, even though the drug did not change AMPH place preference in WT mice,[64] again suggesting that the basis of psychostimulant reward is somewhat different in mice that have experienced a lifelong deletion of the DAT gene. These results indicate that other mechanisms, most likely involving 5-HT, may not play a major role in the rewarding properties of AMPH in WT mice, although the extent of this interaction may be influenced by genetic background, as mentioned earlier, and will require further clarification.

By contrast, the acute locomotor response to AMPH was abolished in these mice under nonhabituated conditions; indeed, reductions in locomotion are often observed in DAT KO mice after administration of AMPH,[43,67] as was the case for cocaine, so that these effects in DAT KO mice are likely to be mediated by SERT, because fluoxetine produced a similar results in these mice.[43,67] Similar changes in response to AMPH are also observed in DAT KD mice.[25] NET may also have a role in these effects because NET KO has been found to increase the locomotor stimulant effects of AMPH.[17] As discussed in the preceding text, locomotor hyperactivity in DAT KO mice has been considered an animal model of AD/HD, an assertion that these "paradoxical" effects of psychostimulants support. Furthermore, these effects are associated with opposite effects of AMPH on postsynaptic signal transduction.[68]

DAT-overexpressing transgenic mice

As was demonstrated for cocaine,[23] overexpression of DAT has been shown to affect responses to AMPH in a separate transgenic line,[69] including increased AMPH CPP, AMPH-induced locomotion, and striatal DA efflux. Interestingly, there were no changes in the locomotor responses to several selective and nonselective DA reuptake blockers in that study, which may indicate that these effects are mediated by other transporters.

VMAT2 KO mice

Although the plasma membrane transporters for the monoamines may be of considerable importance for the actions of AMPH, the ultimate site of action is VMAT2. Gene KO of VMAT2 (heterozygous) has been reported to reduce AMPH CPP.[2] This result is surprising given the finding that VMAT2 KO produces a slight increase in the locomotor stimulant effects of AMPH.[2,27] Because of the apparent importance of both DAT and VMAT2 for the actions of AMPH and METH, we recently examined locomotor activity and sensitization in heterozygous DAT KO mice, heterozygous VMAT2 KO mice, double-heterozygous DAT/VMAT2 KO mice, and WT mice, to evaluate the roles of DAT and VMAT2 in METH-induced locomotor behavior and sensitization.[70] The acute locomotor stimulant effects of METH administration were attenuated in heterozygous DAT KO mice, whereas they were enhanced in VMAT$^{+/-}$ mice; each of these findings is consistent with previous observations with AMPH[2,27,43,67] (by contrast, SERT KO has no effect on AMPH-induced locomotion[71]). The attenuation of the acute effects of METH in DAT KO mice was observed regardless of whether it was combined with heterozygous VMAT2 KO. Although sensitization was observed in all groups, it was substantially attenuated in DAT KO mice, again regardless of whether it was combined with VMAT2 KO. These findings indicate that the heterozygous deletion of DAT produces a major reduction in acute psychostimulant effects of METH, as well as the sensitization of those effects, probably by reducing the ability of METH to enter DA terminals. The mechanism of the VMAT2 effects is less certain. VMAT2 KO reduces both basal and AMPH-stimulated levels of extracellular DA.[27] Thus, these effects may reflect, at least in part, compensatory changes in postsynaptic mechanisms in VMAT2$^{+/-}$ mice, which show increased responses to postsynaptic DA agonists[27] and increased high-affinity DA D_2 receptor function.[29]

Adverse effects of amphetamines

Although addiction is a serious problem for all psychostimulants, neurotoxicity and other adverse consequences of long-term AMPH use is an additional concern, although some AMPH produce more adverse effects than others. METH abuse presents serious health hazards, including irreversible neuronal degeneration, seizures, hyperthermia, and death in humans and experimental animals.[72] METH produces hyperthermia and dopaminergic neurotoxicity in most species examined. Clinical reports and animal studies indicate that lethality from METH closely correlates with hyperthermia, which may be the primary cause of death in cases of overdose. Animal studies suggest that DA receptor activation is crucial for both METH-induced hyperthermia[73] and lethality,[74] although at times there has been an assumption that the METH-induced hyperthermia is 5-HT receptor mediated, as are the hyperthermic effects of MDMA.[75] In a recent study, we examined hyperthermic and lethal toxic effects of METH in DAT, SERT, and DAT/SERT double-KO mice to elucidate the role of these two transporters in METH-induced hyperthermia and lethality.[76] METH caused significant hyperthermia even in mice with one DAT gene copy and no SERT copies, whereas mice with no DAT copies and one SERT gene copy showed significant but reduced hyperthermia when compared to WT mice after METH treatment. These results demonstrate that METH may exert a hyperthermic effect via DAT, or via SERT, without DAT. Double KO of both the DAT and SERT genes eliminated the hyperthermic effects of METH and revealed a hypothermic response. As might be expected given these findings, DAT gene deletion in mice strikingly increased the 50% lethal dose for METH by 1.7-fold compared to WT mice. However, hyperthermia was not solely responsible for lethality, because the mechanisms mediating hyperthermia and toxicity could be dissociated: DAT KO (SERT WT) mice exhibited hyperthermia but greatly reduced METH lethality, and the lethality was not different from DAT/SERT double-KO mice that had hypothermic responses to METH. These findings indicate that DAT may be a more critical mediator of the adverse events associated with METH overdose than SERT.

As mentioned before, a major concern regarding the widespread illicit use of AMPH and METH is their neurotoxic potential, as revealed in animal studies and as observed clinically. This includes both acute adverse events, as discussed earlier, as well as long-term effects of neuronal toxicity and other changes produces by these drugs. In animal models, METH produces dopaminergic,[77] and to a lesser extent serotonergic,[78] neurotoxicity. The neurotoxic effects of METH on DA neurons are eliminated in DAT KO mice,[79] although the effects of METH on serotonergic neurons are attenuated but still present. The neurotoxic effects of METH are enhanced in VMAT2$^{+/-}$ KO mice,[80,81] as are the neurotoxic effects of MPTP[2,82] and L-dopa.[83] Enhanced neurotoxicity was not observed after subchronic treatment with L-dopa in VMAT2$^{+/-}$ KO mice.[84] Increased dopaminergic toxicity after acute treatments with these agents may reflect a generally diminished capacity of VMAT2 to sequester toxins[85] in VMAT2$^{+/-}$ KO mice, as well as increased accumulation of oxidative metabolites resulting from elevated cytosolic DA concentrations. Although homozygous VMAT2 KO is lethal with a few days postnatally, a study that examined early postnatal ventral midbrain cultures from VMAT2$^{+/+}$, VMAT2$^{+/-}$, and VMAT2$^{-/-}$ mice found that there was an inverse relationship between VMAT2 expression and dopaminergic toxicity.[86]

MDMA

MDMA is another commonly abused AMPH compound that produces positive subjective feelings, produces reward, and is associated with several adverse effects including hyperthermia, lethality, and neurotoxicity.[87] The subjective state induced by MDMA is described as qualitatively different from that of other AMPH and is said to include feelings of openness and empathy.[88] Although many of its behavioral and psychological consequences have been associated with its effects on serotonergic function, MDMA increases DA and norepinephrine function as well.[89] There is evidence that MDMA CPP and self-administration depend on DA systems,[90,91] although its affinity for SERT is higher than its affinity for DAT[58] and it produces greater release of 5-HT than DA.[92] Thus, the dopaminergic effects of MDMA are likely to be indirect consequences of MDMA actions. This idea is supported by the demonstration that deletion of the SERT gene eliminates the acquisition of MDMA self-administration.[93] Some of these effects may be open to other interpretations, however. Part of the effect of SERT KO on operant responding for MDMA appeared to be due to more generalized behavioral or cognitive deficits that delayed the acquisition, and maximal response rate, of operant responding for food and water rewards. Indeed, we observed similar deficits for acquisition of cocaine self-administration in SERT KO mice.[19] However, these more general deficits in operant responding can not fully account for the effects of SERT KO on MDMA self-administration, which was abolished, as were the locomotor stimulant effects of MDMA.[71] Deletion of the SERT gene increases basal levels of 5-HT in diverse brain regions but does not affect basal DA levels.[20,94,95] Although the elevations in extracellular DA produced by MDMA in the nucleus accumbens were unaffected by deletion of the SERT gene, MDMA-induced increases in extracellular 5-HT in the prefrontal cortex were abolished,[93] as was 5-HT release in the dorsal raphe and consequent inhibition of serotonergic neurons,[96] indicating that changes in 5-HT in SERT KO mice may have the greatest relevance to the behavioral effects of MDMA discussed earlier.

In addition to its abuse potential, MDMA produces long-term changes in serotonergic neurons that have been described as neurotoxic.[92] The nature of MDMA "neurotoxicity" is a matter of debate, and although it has been suggested that this is, strictly speaking, not the case, substantial impairments in serotonergic functioning are observed.[97] Many of the long-term effects of MDMA administration, including dorsal raphe 5-HT_{1A} supersensitivity, decreased hippocampal cell proliferation, and depressive-like behavior, are all eliminated in SERT KO mice, suggesting that SERT is the primary mediator of these adverse effects as well.[96] Of course, one interpretive problem for some of these effects is that SERT KO mice, in some respects, have baseline phenotypes characteristic of WT mice chronically treated with MDMA to begin with. Other genes are important in the neurotoxic effects of MDMA as well. MDMA-induced 5-HT depletion is eliminated in MAO-B KO mice,[98] and even more interesting, in these mice DA depletion is enhanced.

Methylphenidate

Methylphenidate is a nonspecific monoamine reuptake blocker with a greater affinity for NET than cocaine, but a relatively weak affinity for SERT,[99] and the prototypical AD/HD treatment. As with other monoamine blockers, the relative importance of methylphenidate binding to different monoamine transporters for its behavioral effects is a matter of some debate. As discussed, DAT KO produces impairments in PPI that can be ameliorated by cocaine and AMPH. If this is indeed a model of AD/HD, at least in certain respects, then it should be expected that methylphenidate should also ameliorate these attentional deficits. Indeed, methylphenidate was found to ameliorate DAT KO induced PPI deficits[51] and hyperactivity.[43] In WT mice, methylphenidate produces activation of the *c-fos* in diverse brain areas that are not activated in DAT KO mice,[100] whereas DAT KO mice have activation of the *c-fos* in brain areas that are not normally activated in WT mice. This different pattern of *c-fos* activity in WT and DAT KO mice was thought to reflect dopaminergic, versus nondopaminergic, mechanisms of methylphenidate and are consistent with the different behavioral effects of methylphenidate in these mice. The locomotor-decreasing effects of methylphenidate in hyperactive DAT KO mice may also be associated with the opposite effects of AMPH on postsynaptic signal transduction compared to WT mice.[68]

Although some responses to methylphenidate are substantially altered in DAT KO mice, the rewarding effects of methylphenidate in the CPP paradigm are unaffected,[3] similar to the effects of cocaine in these mice. As discussed in a previous section, some of these effects are probably due to neurodevelopmental or compensatory alterations in DAT KO mice, because similar changes are not observed in the DAT CI mouse. The DAT CI mutant mouse has reduced binding of methylphenidate to the DAT,[101] and the rewarding effects of methylphenidate in the CPP paradigm, as well as the locomotor stimulant and stereotypical effects of methylphenidate, were all eliminated in these mice.

Methylphenidate has a low affinity for SERT, although it does bind to both DAT and NET.[99] Thus, those effects not mediated by DAT are likely to be mediated by NET. Gu *et al.*[102] recently identified a mutant mouse with a cocaine-insensitive NET. Interestingly, the triple mutation in this mouse line resulted in a substantial reduction in binding of cocaine, but it had little effect on the affinity for AMPH or methylphenidate and had relatively normal norepinephrine transport.

Monoamine receptor knockouts

With the substantial evidence for the involvement of monoamine transporters in the effects of psychostimulant drugs, it is not surprising that there is also substantial evidence for the involvement of monoaminergic receptors. As for transporters, much of this research has reflected a dopaminergic emphasis (or bias, perhaps), at least initially, both in the pharmacological literature and in transgenic studies. As can be seen in Table 3, most studies have concentrated on the rewarding and locomotor-stimulant effects of cocaine in dopaminergic receptors, with much less work examining other psychostimulant effects and other monoaminergic receptors.

Table 3. Psychostimulant responses in monoamine transporter transgenic mice

Citation	Gene	Drug	Micro-dialysis	Loco-motion	CPP	Self-administration	Adverse effects
Budygin, E.A. *et al.* 2004	DAT KO	AMPH			Unaffected, abolished by 5-HT_{1A} antagonist		
Salahpour, A. *et al.* 2008	DAT over-expression	AMPH	Increased	Increased	Increased		
Spielewoy, C. *et al.* 2001	DAT KO	AMPH		Decreased			
Xu, F. *et al.* 2000	NET KO	AMPH		Increased			
Takahashi, N. *et al.* 1997; Fukushima, S. *et al.* 2007	VMAT2 KO	AMPH, METH		Increased	Decreased		
Numachi, Y. *et al.* 2007	DAT KO	METH					Reduced hyper-thermia
Fumagalli, F. *et al.* 1998	DAT KO	METH					Eliminated neurotoxic effects
Fumagalli, F. *et al.* 1999; Guillot, T.S. *et al.* 2008	VMAT2 KO	METH					Enhanced neurotoxic effects
Trigo, J.M. *et al.* 2007	SERT KO	MDMA	Abolished 5-HT in PFc			Eliminated	
Bengel, D. *et al.* 1998	SERT KO	MDMA		Eliminated			
Renoir, T. *et al.* 2008	SERT KO	MDMA					Decreased hippocampal cell proliferation was eliminated
Sora *et al.* 1998	DAT KO	Methyl-phenidate			Unaffected		
Tilley, M.R. & H.H. Gu. 2008	DAT CI	Methyl-phenidate		Eliminated	Eliminated		

PFc: prefrontal cortex.

Dopamine receptors

The studies of DAT KO mice discussed herein obviously implicate dopaminergic mechanisms in many psychostimulant effects but do not specify which DA systems are involved. Because of the belief of the importance of DA for psychostimulant effects, some of the first gene KO mice made were for dopaminergic receptor genes. Dopaminergic receptors are classified as D_1-like (D_1 and D_5) or D_2-like (D_2, D_3, and D_4) receptors on the basis of sequence homology and pharmacology.[103] DA receptors also have different distributions in the brain.[104–108] This would then indicate that transgenic manipulations of dopaminergic receptors may produce more specific effects on behavior, and the effects of psychostimulants, than monoamine transporter manipulations. However, it may also be possible that there is a greater possibility of compensation by other receptors in the absence of one.

Cocaine

D_1 KO mice. There is substantial pharmacological evidence for the involvement of DA receptors in drug reward, and in the effects of cocaine in particular. Full D_1-like agonists are self-administered by rats,[109] and administration of D_1-like antagonists decreases cocaine self-administration.[110] Of course one problem with many pharmacological agents used to study dopaminergic effects is specificity for DA receptor subtypes, so that the effects mentioned earlier may not be due to actions at D_1 receptors per se. Transgenic techniques thus presented a way to specifically address which DA receptor subtypes may be involved in the rewarding effects of cocaine. D_1 KO mice have been reported to demonstrate normal responses to the rewarding effects of cocaine in the CPP paradigm,[111] although they do show reduced voluntary ethanol consumption,[112] suggesting that deletion of the D_1 receptor does attenuate the reinforcing properties of some drugs. Interestingly, and in a manner somewhat reminiscent of the consequences of deletion of the DAT gene, the locomotor stimulant effects of cocaine, as well as locomotor sensitization, are eliminated in D_1 KO mice.[111,113,114] Indeed, this parallel may go even further, because D_1 KO mice have been reported to have locomotor-decreasing effects of cocaine.[115] Although another study did not observe this, it did observe locomotor-decreasing effects of cocaine in combined D_1–D_3 KO mice, which were hyperactive at baseline.[116] Combined D_1–D_3 KO also reduced cocaine CPP, but only at the lowest dose examined.[116] Despite the observation of normal cocaine CPP in D_1 KO mice, cocaine self-administration is virtually eliminated, most of the subjects not meeting the criteria for acquisition.[117] Again, this situation is similar to that observed in DAT KO mice in a recent study.[19] In WT mice the immediate early genes *c-fos* and *zif268* are activated by cocaine, but this does not occur in D_1 KO mice, and instead there is activation of the expression of the substance P gene.[118] D_1 KO also reversed the effect of cocaine on CREB phosphorylation, producing decreases, rather than increases, in CREB phosphorylation,[116] and a reduction in the number of pCREB immunoreactive cells were observed throughout the striatum in these mice.

D_2 KO mice. On the basis of pharmacological evidence alone, there is perhaps even more evidence for the involvement of the D_2 receptor in the rewarding effects of psychostimulants. Similar to D_1-like DA receptors, D_2-like agonists are self-administered by rats[109] and D_2-like antagonists reduce cocaine reinforcement.[119] However, despite the indications from pharmacological studies, self-administration of low to moderate doses of cocaine is unaffected, whereas self-administration of moderate to high doses of cocaine is actually increased in D_2 KO mice,[119] and D_2 KO produced only a slight reduction in cocaine CPP.[120] Those authors also found a reduction in the ability of cocaine to stimulate production of c-Fos. D_2 KO also does not affect the discriminative stimulus effect of cocaine.[121] Thus, it would appear at the very least that D_2 KO does not produce quite the same effects as D_2 antagonists in WT mice in models of drug reward. Whether this indicates that there are compensatory changes in other DA receptors, or that normally multiple receptors are involved, remains to be determined.

Similarly to the effects discussed in the foregoing section, locomotor stimulant effects of cocaine were largely unaffected in D_2 KO mice, once differences in basal activity were taken into account,[121] although another study did find reduced locomotor-stimulant effects of cocaine,[120] which was accompanied by pronounced stereotypical grooming. DA autoreceptor function was eliminated in D_2 KO mice,[122] but cocaine-mediated DA efflux was only slightly affected in striatal synaptosomes. This outcome was observed even though DAT clearance rates were reduced by 50%,[123] which seemed to result from a change in activity because the density and affinity of DAT sites were unchanged. In any case, regardless of the mechanism, these changes are associated with substantially increased DA release in response to cocaine as measured by *in vivo* microdialysis in D_2 KO mice, or mice with a selective deletion of the long isoform of the D_2 (D_{2L}) receptor.[124]

D_3, D_4, and D_5 KO mice. There has been less pharmacological evidence of a role for other DA receptor subtypes in the effects of psychostimulants, although certainly some, and perhaps more for the D_3 receptor,[125] because more selective agents have not been available for as long. Thus, examination of genetic deletion of the other DA receptors should be especially illuminating here. Both D_3 KO mice[126] and D_4 KO mice[127,128] have increased locomotor responses to cocaine. By contrast, D_5 KO was reported to produce a reduction in cocaine-stimulated locomotion,[129] although this effect was not found in another study.[114] The basis of the effects in D_3 and D_4 KO mice was suggested to be quite different. D_3 KO mice have increased sensitivity to combined D_1 and D_2 agonists, so it was suggested that the enhanced responses to cocaine in these mice were due to increased D_1/D_2 synergy.[126] In contrast, the effects of D_4 gene deletion were suggested to be mediated by the elimination of inhibitory effects of the D_4 receptor.[116] In either case the mechanisms involved are somewhat speculative. The baseline difference in cocaine responsiveness observed in D_3 KO mice discussed in the preceding section was not large and limited to a low dose. Using a higher dose and testing in the home cage, another study found that D_3 KO mice had reduced locomotor responses to cocaine, although this appeared to be the result of stereotypical head-bobbing behavior.[130] Furthermore, in WT mice repeated cocaine treatment produced locomotor sensitization, but this was not found in D_3 KO mice, which instead showed sensitized stereotypical head bobbing.[130] The increased stereotypy observed in D_3 KO mice is also associated with increased stimulatory effects on *c-fos* and dynorphin gene expression,[130] which were thought to be indicative of enhanced D_1 stimulation in the absence of D_3. In contrast to diminished effects on cocaine locomotion, D_3 KO mice exhibit increased sensitivity to cocaine in the CPP paradigm.[126] Reduced locomotor sensitization was observed in D_5 KO mice,[114] which did not exhibit sensitization under most conditions tested.

Far less work has been done to examine other psychostimulant effects. The potency of cocaine as a discriminative stimulus was enhanced in D_4 KO mice[127] but unaffected by D_5 KO.[129] Cocaine CPP was also normal in these mice.[114] The ability of cocaine to produce conditioned locomotion is not different in D_3 KO mice compared to WT control mice,[131] although those authors found that D_3 agonists did inhibit the behavior, again suggesting compensatory actions of other DA receptors when one is eliminated. The effects of cocaine on PPI appear to involve DA D_1, D_2, and D_3 receptors.[132] D_1 KO eliminated cocaine-induced impairments in PPI, whereas D_2 KO was partially effective. By contrast, D_3 KO produced increases in cocaine-induced impairments in PPI. Finally, DA receptors may also play a role in cocaine-induced toxicity. Although D_3 KO did not affect cocaine-induced convulsions by itself, it did block the protective effects of a D_2/D_3 agonist, whereas D_2 KO was without effect.[133]

Much more work remains to be done here. Many of the effects of psychostimulants that have been identified in DAT KO mice have not been examined in DA receptor KO mice. Furthermore, as for monoamine transporter KOs, it may be necessary to examine multiple receptor KOs where there is no or little effect of single receptor gene KOs.

Amphetamines

As for cocaine, most transgenic work has concentrated on dopaminergic receptor KOs, as can be seen in Table 4. Most studies have concentrated on the rewarding and locomotor-stimulant effects of AMPH, with much less work examining other psychostimulant effects and other AMPH compounds.

D_1 KO mice. There are conflicting reports on the effects of AMPH in D_1 KO mice. An early study found that although initial locomotor responses to AMPH were unaltered in D_1 KO mice, the sensitization of these responses was diminished.[134] Another study found a slight diminution in the acute locomotor-stimulating effects and largely unaltered locomotor sensitization,[17] although one difficulty of interpretation here was high locomotor activity in saline-treated subjects, so that when this is taken into account, it could be considered that they have reduced sensitization. Contrary to these studies,

Table 4. Psychostimulant responses in monoamine receptor transgenic mice

Citation	Gene	Drug	Locomotion	Sensitization	CPP	PPI	Adverse effects: hyperthermia	Adverse effects: lethality
Crawford, C.A. *et al.* 1997	D_1 KO	AMPH	Unaffected	Decreased				
Karper, P.E. *et al.* 2002	D_1 KO	AMPH		Unaffected				
McDougall, S.A. *et al.* 2005	D_1 KO	AMPH	Increased	Increased				
Ralph, R.J. *et al.* 1999	D_2 KO	AMPH				Disrupted AMPH-induced impairments		
Kelly, M.A. *et al.* 2008	D_2 KO	AMPH	Decreased	Unaffected				
Xu, R. *et al.* 2002	D_{2L} KO	AMPH				Unaffected AMPH-induced impairments		
Xu, M. *et al.* 1997	D_3 KO	AMPH	Increased					
Ralph, R.J. *et al.* 1999	D_3 KO	AMPH				Unaffected AMPH-induced impairments		
Ralph, R.J. *et al.* 1999	D_4 KO	AMPH				Unaffected AMPH-induced impairments		
Kruzich, P.J., K.L. Suchland & D.K. Grandy. 2004	D_4 KO	AMPH		Increased				
Kelly, M.A. *et al.* 2008	D_4 KO	AMPH	Increased					
Harrison, S.J. & J.N. Nobrega. 2009	D_5 KO	AMPH		Increased				
Bronsert, M.R. *et al.* 2001	5-HT_{1B} KO	AMPH	Increased	Increased				
Weinshenker, D. *et al.* 2002	DBH KO	AMPH	Increased	Unaffected				
Drouin, C. *et al.* 2002	α_{1b} KO	AMPH	Decreased	Decreased				

Continued.

Table 4. *Continued*

Citation	Gene	Drug	Locomotion	Sensitization	CPP	PPI	Adverse effects: hyperthermia	Adverse effects: lethality
Sallinen, J. *et al.* 1998	α_{2c} KO	AMPH	Increased	Increased				
Lahdesmaki, J. *et al.* 2004	α_{2A} KO	AMPH				Increased AMPH-induced impairments		
Ito, M. *et al.* 2008	D_1 KO	METH					Modestly attenuated METH-induced hyperthermia	Substantially attenuated METH-induced lethality
Ito, M. *et al.* 2008	D_2 KO	METH					Eliminated METH-induced hyperthermia	Substantially attenuated METH-induced lethality
Rubinstein, M. *et al.* 1997	D_4 KO	METH	Increased					
Allan, A.M. *et al.* 2001	5-HT_3 overexpression	METH			Decreased			
Risbrough, V.B. *et al.* 2006.	D_1 KO	MDMA	Increased					
Risbrough, V.B. *et al.* 2006.	D_2 KO	MDMA	Decreased					
Risbrough, V.B. *et al.* 2006.	D_3 KO	MDMA	Unaffected					
Dulawa, S.C. *et al.* 1998, 2000	5-HT_{1B} KO	MDMA				Increased		
Scearce-Levie, K., S.S. Viswanathan & R. Hen. 1999	5-HT_{1B} KO	MDMA	Decreased			Increased		
Bexis, S. & J.R. Docherty. 2005	α_{2A} KO	MDMA					Biphasic response, hypothermia followed by hyperthermia	

another study found generally increased responses to AMPH after chronic treatment in D_1 KO mice, including increased context-dependent sensitization, context-independent sensitization, and conditioned locomotion.[135] Yet another study found no differences in sensitization in D_1 KO mice.[136] It is difficult to say why these different results have been obtained.

D_2 KO mice. One complication of the study of D_2 KO mice is that the D_2 receptor is expressed both presynaptically and postsynaptically. DA autoreceptor function is eliminated in D_2 KO mice,[122] although interestingly the effects of AMPH on DA release were unaltered in that study. Interpretation of psychomotor stimulant effects in D_2 KO mice is complicated by reduced basal levels of activity.[137] However, even when this is taken into account they do appear to display diminished locomotor-stimulant effects of METH,[138] although sensitization of those responses did not appear to be affected.

D_3, D_4, and D_5 KO mice. As for cocaine, both D_3 and D_4 KO mice have increased locomotor-stimulant effects of AMPH,[126,139] although this is limited to particular doses.[140] Importantly, these changes in D_3 KO mice were not associated with changes in the stereotypical effects of AMPH,[140] as might be predicted based on the localization of that receptor compared to the D_2 receptor. D_4 KO mice also have increased locomotor responses to METH.[128] The mechanisms may be different in each case, as discussed earlier, and may or may not involve other DA receptors. Locomotor sensitization to AMPH is also enhanced in D_4 KO mice,[139] at least under some conditions. AMPH sensitization was not different from WT controls in D_5 KO mice.[141]

The PPI-impairing effects of AMPH were disrupted in D_2 KO mice but not D_3 or D_4 KO mice.[142] This pattern is slightly different from that discussed earlier for cocaine. This is a further indication that the effects of psychostimulants, though substantially overlapping, still involve some different mechanisms. The effect of AMPH was not disrupted in D_{2L} KO mice, which may suggest that these effects are mediated by the D_{2S} isoform.[143]

Adverse effects of AMPH. Evidence for the importance of DA in the adverse effects of METH was discussed earlier, including data from DAT KO mice, including evidence that the hyperthermic and lethal effects of METH were somewhat dissociable. DA antagonists reduce METH-induced hyperthermia[73] and lethality,[74] but these effects are highly dose dependent and substantially dependent on ambient temperature. In a recent study, we examined the roles of dopamine D_1 and D_2 receptors in METH-induced hyperthermia and lethal effects by using D_1 KO and D_2 KO mice.[144] This study found that both the D_1 and D_2 receptors have roles in the lethal effects of METH but differently affect the hyperthermic effects of METH. D_2 KO eliminated METH-induced hyperthermia, whereas D_1 KO produced a more modest attenuation of this response. Both KOs produced a substantial attenuation of METH-induced lethality. These data further dissociate the mechanisms underlying METH-induced lethality and METH-induced hyperthermia, even though dopaminergic mechanisms appear to be involved in both effects.

MDMA. Most research into the mechanisms underlying the effects of MDMA has concentrated on serotonergic mechanisms, but there is also evidence for direct or indirect roles of dopaminergic systems in MDMA-induced effects, although not much work has been done in this area in transgenic mice. In male D_1 KO mice the locomotor stimulant effects of MDMA were increased, whereas D_2 KO was found to reduce MDMA effects and D_3 KO was without effect.[145] There were also some changes in the pattern of activity, including reduced MDMA-induced perseverative thigmotaxis in D_2 KO mice. There was also some sex dependency of these effects, so although D_3 KO was without effect in males, there was a slight reduction in MDMA-induced hyperlocomotion in females.

Serotonin receptors

Although the importance of dopaminergic systems in the effects of psychostimulants has been well established, data discussed earlier indicate that serotonergic systems, particularly those that interact with dopaminergic systems, also have a role. That evidence has not identified the particular parts of the serotonergic system that may be involved in psychostimulant actions and which of the many 5-HT receptor subtypes may be involved. 5-HT receptors are diverse, comprising many structurally and pharmacologically distinct mammalian 5-HT receptor subtypes, as determined from sequence homology and pharmacology,[146] which have distinctly different anatomical distributions,[147–149] and many of which are thought to modulate the effects of psychostimulants.[150] Although pharmacological evidence has been important in implicating 5-HT in the effects of many psychostimulants, because of the many 5-HT receptor subtypes the situation regarding specificity of available agents is even more of a problem than it is for dopaminergic systems. Therefore, transgenic studies have contributed substantially to our knowledge about the role of specific 5-HT receptor subtypes in the effects of psychostimulants, although some have been much more thoroughly investigated than others.

Cocaine

5-HT_{1B} KO mice. On the basis of the impetus of pharmacological evidence, the 5-HT_{1B} receptor has been more extensively examined in transgenic studies than other 5-HT receptor subtypes. This evidence includes data demonstrating that 5-HT_{1B} receptor agonists enhance cocaine-induced reinforcement[151] and increase extracellular DA in the nucleus accumbens.[152] 5-HT_{1B} KO increased the locomotor stimulant effects of cocaine,[15,153] which prompted Rocha *et al.*[15] to suggest that these mice were "presensitized" to cocaine. 5-HT_{1B} KO was initially associated with accelerated acquisition of cocaine self-administration,[154] without many other changes, but was subsequently associated with increased cocaine self-administration under a variety of conditions.[15,153] Surprisingly, cocaine was reported not to produce a CPP in these mice,[155] although this appears to be yet another example in which transgenic manipulations produce divergent results in CPP and self-administration paradigms. Nonetheless, as further evidence that these effects involved interactions with dopaminergic systems, *in vivo* microdialysis studies found that basal and cocaine-evoked DA levels in the nucleus accumbens of 5-HT_{1B} KO mice were increased.[156] These changes would appear to be most consistent with the self-administration studies in these mice, although there is evidence that postsynaptic changes may oppose these actions, including reduced cocaine-evoked elevation of c-Fos,[157] which may help explain the divergent effects in different models.

Other serotonin receptors. Other 5-HT receptor subtypes have been much less extensively examined in transgenic models, the initial studies beginning with 5-HT receptor subtypes localized on dopaminergic neurons and for which there was already evidence that they modulate dopaminergic function.[158] Deletion of 5-HT_{2C} receptors was associated with greater release of DA in the nucleus accumbens and increased reinforcing efficacy of cocaine, including increased responding under a progressive ratio schedule.[159] In both 5-HT_{1B} receptor KO mice and in 5-HT_{2C} receptor KO mice, higher reinforcing efficacy of cocaine was associated with greater cocaine-stimulated DA levels in the nucleus accumbens. Thus studies of cocaine self-administration in different 5-HT receptor KO mice suggest that increased reinforcing efficacy of cocaine is ultimately associated with increased DA activity.

Some other 5-HT receptor subtypes have also been examined. The locomotor-stimulating effects of cocaine are increased in 5-HT_{2A} KO mice, but they still exhibit sensitization.[160] Transgenic overexpression of the 5-HT_3 receptor reduces the rewarding effects of cocaine in the CPP paradigm.[161] In these data there was a slight trend for 5-HT_3-overexpressing mice to be more sensitive to low doses of cocaine. The 50% effective dose for locomotor-stimulating effects of cocaine was substantially reduced in these mice, which was associated with greater DA release in response to application of low doses of cocaine to striatal brain slices. The contribution of specific serotonergic receptors to the toxic or lethal effects of cocaine has not been investigated to any great degree, although a recent study has shown that 5-HT_7 KO increases cocaine-induced seizures and lethality.[162]

Amphetamines

Other psychostimulants have been even less examined than cocaine in 5-HT receptor KO mice. 5-HT_{1B} KO mice had increased acute and sensitized locomotor effects of AMPH.[163] On the basis of comparisons between intraperitoneal and intravenous routes of administration, those authors suggested that some of the effects of 5-HT_{1B} KO were due to interactions with handling stress, but not all. As for cocaine, the 50% effective dose for the locomotor-stimulating effects of METH was decreased in 5-HT_3-overexpressing mice.[161] Finally, MDMA does not affect PPI in WT mice but increases PPI in 5-HT_{1B} KO mice,[164,165] whereas the locomotor stimulant effects of MDMA are attenuated in 5-HT_{1B} KO mice.[166]

Norepinephrine system

Norepinephrine systems have been the least associated with the rewarding effects of psychostimulants of the three main monoamine systems, at least in recent years. However, as discussed in the preceding, NET KO affects several psychostimulant-induced behaviors, including psychostimulant reward. Although not extensively investigated, there is accumulating evidence for involvement of norepinephrine systems in several psychostimulant responses from recent transgenic studies. At least a part of the impetus for examining particular norepinephrine receptors comes from evidence that these receptors modulate somatodendritic DA function.[167]

Cocaine

Transgenic mice that lack the enzyme that synthesizes norepinephrine, DA β-hydroxylase (DBH), are hypersensitive to the locomotor-stimulant effects of cocaine.[168] There was also a leftward shift in the dose–response curve for cocaine CPP, with a greater CPP observed in DBH KO mice at a cocaine dosage of 5 mg/kg, as well as a pronounced cocaine conditioned place aversion at 20 mg/kg cocaine. These authors suggested that this change in responsiveness was due to profound adaptive changes in DA systems, including substantially reduced presynaptic dopaminergic responses and postsynaptic receptor supersensitivity caused by increased numbers of both D_1 and D_2 receptors in the high-affinity state. Furthermore, these effects were observed in the striatum, but not the prefrontal cortex. The reason for these differences is uncertain, as is the degree to which the adaptations may be driven, or prevented in the prefrontal cortex, by DA release from norepinephrine synapses. Another report suggested that DBH KO eliminated the rewarding effects of cocaine in the CPP paradigm,[169] but this might be due to the dose–effect relationship noted earlier. The specific receptors involved in these effects is uncertain and will remain so until more noradrenergic receptor subtypes have been investigated, but initial evidence implicates the α_{1b} receptor. Oral cocaine consumption was reduced by α_{1b} KO, and there were substantial decreases in the locomotor-stimulant effects of cocaine as well as locomotor sensitization.[170]

Surprisingly, few studies have addressed the aversive effects of cocaine, which are often presumed to involve noradrenergic mechanisms. However, a recent report has found that the aversive effects of cocaine are eliminated in DBH KO mice.[171] With regard to lethal or toxic effects, again, not much has been done, but DBH KO had no effect on cocaine-induced seizures.[172]

Amphetamines

DBH KO mice are hypersensitive to the locomotor-stimulant effects of AMPH and exhibited a leftward shift in the dose–response curve for AMPH, including exhibiting stereotypical behavior at much lower doses of AMPH than is observed in WT mice.[173] However, this may have resulted from alterations in DA receptor function because these mice were less sensitive to a D_1 agonist and more sensitive to a D_2 agonist. Sensitization of AMPH responses was unaltered in these mice. Indeed, norepinephrine may have a more general modulating effect upon dopaminergic function and the effects of psychostimulants. Recent pharmacological studies have suggested that stimulation of the α_{1b} receptor increases psychostimulant effects, whereas stimulation of the α_2 adrenergic receptor inhibits those effects.[174] This supposition has been supported by transgenic studies. α_{1b} KO produces substantial decreases in the locomotor stimulant effects of AMPH as well as sensitization of those responses,[170] whereas the locomotor-stimulant effects of AMPH are enhanced in α_{2c} KO mice and reduced by transgenic overexpression of the α_{2c} receptor.[175] Consistent with the evidence for the involvement of both SERT- and NET-mediated responses underlying the retention of CPP in DAT KO mice,[18] there is evidence in α_{1b} KO mice for compensatory involvement of 5-HT systems. In α_{1b} KO mice a 5-HT_{2A} antagonist blocked the locomotor-stimulant effects of AMPH and the sensitization of those effects.[176] Under normal circumstances these two receptors have been suggested to be mutually inhibitory, even though they are individually behaviorally activating, and one mechanism of sensitization has been suggested to be the decoupling of these receptors producing increased DA activity.[177]

Again, little work has been done on the role of noradrenergic system genes in other psychostimulant effects. Adrenergic receptors may contribute to the effect of AMPH on sensorimotor gating in the PPI model. Consistent with some of the other effects discussed earlier, α_{2A} KO mice have increased PPI-disrupting effects of AMPH.[178] α_{2A} KO also alters the effects of MDMA on temperature.[179] Finally, with regard to adverse effects of amphetamines, elimination of norepinephrine in DBH KO mice increases the effect of METH on DA release, oxidative stress, and neurotoxicity.[180]

Discussion

From the data presented here it is clear that there is accumulating evidence from transgenic, and especially gene KO studies, for the role of monoaminergic transporter and receptor genes in the actions of psychostimulants, and by implication addiction. This review has been limited in two major ways: to discussion of the effects of transgenic manipulations of monoamine transporter and receptor genes and to the effects of psychostimulants. There is substantial evidence that monoamine gene manipulations also affect the actions of addictive drugs that do not act directly through monoamine transporters or receptors, such as morphine and ethanol, and similarly, there is a substantial body of work demonstrating that transgenic manipulations of genes other than those discussed here affect the actions of psychostimulants. However, what is evident from the transgenic work discussed here is that there is a complex emerging picture of interactive gene effects, even when considering just the monoaminergic genes, that is important in determining the effects of psychostimulants.

An additional point that has been substantially sidestepped in this review is the relationship of these transgenic "models" to human addiction. One of the conclusions that has become most evident in recent genomewide association studies of addiction[181–187] is that the genes that underlie addiction in humans seem to rather rarely include the classes of genes discussed here, monoamine transporters and receptors. Instead, the allelic variation in the actual human population that seems to underlie addiction involves a higher proportion of other classes of genes, including many involved in signal transduction and synaptic plasticity.[188] This realization will be important for developing animal models of addiction, and as the sophistication of these approaches develops, for modeling the specific allelic variants that may underlie human addiction.

This is not to say that the extensive studies discussed here have not contributed a great deal to the study of addiction. First, these transgenic models indicate genes that may be involved in addiction in humans (this may or may not be the case depending upon the actual allelic variation that exists in these genes in humans). Second, they indicate genes that, when manipulated, produce substantial changes in observable phenotypes that are relevant for addition, and the many diverse actions of psychostimulants, and may therefore contribute to the development of addiction therapeutics. Thus, in these ways the use of transgenic techniques has substantially improved our understanding of addiction genetics and provides insight into the polygenic determination of drug addiction phenotypes in ways that would not be possible with other methods. The complex picture that has emerged from this research fits with recent polygenic descriptions of genetic influences on human addiction developed from genomewide association studies, and no matter how much we may desire simple answers to our questions, we must accept the complex reality that is evident in these data.

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Conflicts of interest

The authors declare no conflicts of interest.

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