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Stimulant and reinforcing effects of cocaine in monoamine transporter knockout mice

Beatriz A. Rocha*

Merck Research Laboratories, Department of Pharmacology, RY80Y-140, P.O. Box 2000, Rahway, NJ 07065, USA

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Abstract

A large body of evidence supports the hypothesis that the reinforcing effects of cocaine depend on its ability to block the dopamine transporter (DAT), thereby increasing dopamine extracellular concentration within the mesocorticolimbic system. However, the fact that cocaine similarly binds to the serotonin and norepinephrine transporters (SERT and NET, respectively), raises the possibility that modulation of mesocorticolimbic dopaminergic transmission might be achieved through alternate pathways. The successful disruption of the genes coding for the DAT, the SERT and the NET offered ideal tools to determine the extent of the participation of these transporters and respective monoaminergic systems in the reinforcing effects of cocaine. Studies of cocaine-induced motor activation and maintenance of intravenous (i.v.) self-administration in DAT- and in NET-knockout (KO) mice are reviewed here, and discussed in light of new observations obtained from double monoamine transporters KO mice (i.e., DAT-KO/SERT-KO, NET-KO/SERT-KO). The reinforcing potency of cocaine is maintained in the absence of the DAT but decreased in the absence of the NET; its motivational rewarding effect is observed in the absence of the SERT, but not when both DAT and SERT are lacking. Moreover, a dichotomy between cocaine motor activating and reinforcing effects is reported. Such dichotomy is suggestive of independent mechanisms underlying the psychomotor stimulant and reinforcing effects of cocaine. Overall, these studies provide evidence that cocaine dynamically acts at multiple sites through pathways that might be exchangeable under certain circumstances.

Keywords: Reinforcement; Cocaine self-administration; Hyperactivity; Behavioral sensitization; Knockout, mouse; DAT (dopamine transporter); NET (norepinephrine transporter); SERT (serotonin transporter)

1. Introduction

Cocaine abuse remains a critical challenge for society. One million Americans aged 12 years or older were estimated to be dependent on cocaine in 2000, when 361,000 new users were reported (2001 National Household Survey on Drug Abuse, NHSDA/SAMHSA/Department of Health and Human Services, Bethesda, MD). Economic burden, social order and public health consequences of such scenario are severe, but no specific treatment has yet been approved for cocaine addiction. The reduction of such treatment gap demands, in great part, a better understanding of the neuropathways and mechanisms implicated in the effects of cocaine.

Innovative research in cocaine abuse has been aggressively pursued and has flourished in the last decade, in particular, due to the rapid advance in genetics and the successful generation of mice lacking specific genes. Noteworthy was the generation of mice lacking one or two of the molecular targets of cocaine (Giros et al., 1996; Xu et al., 2000; Sora et al., 1998; 2001; Hall et al., 2002), which are the dopamine transporter (DAT), the norepinephrine transporter (NET), and the serotonin transporter (SERT). These are responsible, respectively, for the uptake of dopamine, norepinephrine and serotonin (5-HT), from the synapses into nerve terminals. The overall behavioral analysis and neurochemical evaluation of the DAT-, NET- and SERT-knockout (KO) mice, which are reviewed elsewhere (Gainetdinov and Caron, 2003; Stephens et al., 2002; Uhl et al., 2002) as well as in other articles of this issue, has been extremely valued in expanding the knowledge of cocaine's molecular actions.

The present review centers on reports assessing the psychomotor stimulant and reinforcing effects of cocaine

* Tel.: +1-732-594-3804; fax: +1-732-594-3841.
E-mail address: beatriz_rocha@merck.com (B.A. Rocha).

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in some of these mutants, and more specifically, in data obtained from experiments describing cocaine-induced motor activation and self-administration.

2. The predictive value of cocaine-induced hyperactivity and reinforcement in laboratory animals—the dopaminergic mesocorticolimbic system

2.1. Motor behavior

As a psychostimulant drug, cocaine, characteristically, elicits a dose-dependent increase in motor ambulatory activity in rodents (Snoddy and Tessel, 1985; Nielsen and Scheel-Kruger, 1988). This hyperactivity is more prominent at low doses, and decreases at higher doses where stereotyped repetitive behavior appears (Tyler and Tessel, 1979). At very high doses, gradual loss of righting reflexes occurs which is rapidly followed by clonic seizures and death (Benowitz, 1993; Matsumoto et al., 1997). These motor effects have extensively been used as behavioral markers for cocaine's pharmacological efficacy, potency, and toxicity.

Besides the dose, cocaine-induced motor effects depend on the number and duration of administration, with repeated administration of subthreshold doses resulting in increased motor (behavioral sensitization) or convulsive (pharmacologic kindling) responses (Schenk and Partridge, 1997; Cromwell et al., 1998; Robinson and Berridge, 1993; Stripling and Ellinwood, 1977). In humans, also depending on the number and duration of drug administration, cocaine can induce addiction as well as a different array of manic syndromes. Consequently, the study of these progressive behaviors in animals has provided insights into neuroplastic adaptations underlying the progression of addiction (Self and Nestler, 1995; Robinson and Berridge, 1993; Nestler and Aghajanian, 1997) and manic syndromes in man (Post and Weiss, 1989).

Stimulant-induced motor activation has often been associated with increased extracellular levels of dopamine within the mesocorticolimbic system, which consists of projections from the midbrain ventral tegmental area to forebrain regions including the nucleus accumbens and the prefrontal cortex. Increased dopamine in the nucleus accumbens has been most implicated in cocaine motor activation (Sharp et al., 1987; Kuczenski et al., 1991), but several evidences of other neurotransmitters mediation, such as glutamate, also exist (Cornish and Kalivas, 2001; Carlezon and Nestler, 2002). Cocaine-induced behavioral sensitization in rats has been correlated with increase of glutamate in the nucleus accumbens (Pierce et al., 1996), and dopamine D1 receptors potentiation of glutamate NMDA receptors responses in striatum and prefrontal cortex have also been described (Seamans et al., 2001), with coactivation of dopamine-glutamate transmission in the prefrontal cortex being implicated in storage of cellular information through increase of long-term potentiation (Gurden et al., 2000).

Through the studies of the neurobiology and circuitry of the motor effects of drugs emerged the concept that the strength of the psychostimulant properties of a drug would predict the strength of its reinforcing or addictive effects (Wise and Bozarth, 1987). More recently, as described below, studies from DAT- and NET-KO mice, showed dichotomies between the psychostimulant and the reinforcing effects of cocaine, and further suggested that, under certain circumstances, it is likely that distinct mechanisms underlie the motor and reinforcing effects of cocaine.

2.2. Self-administration

Based on the operant notion of reinforcement introduced by Skinner (1938), the reinforcing effect of a drug is, by definition, the one that increases the probability that the animal will perform a task in order to self-administer the drug again. In rats, the reinforcing effect of cocaine was first characterized by Pickens and Thompson (1968) when they showed these animals could learn to press a lever in order to receive an intravenous (i.v.) injection of cocaine. More importantly, using saline substitution for cocaine, they demonstrated that lever pressing behavior was dependent on the contiguous relationship between the response and the consequence. Subsequently, cocaine was demonstrated to function as a positive reinforcer to maintain self-administration in a variety of species, by different routes of administration, under several schedules of reinforcement and doses, and was universally established by its power of reproducing in laboratory animals human drug taking (for review, see Johanson and Fischman, 1989; Johanson and Schuster, 1981).

Even though cocaine is self-administered through several different routes, the i.v. route has been extensively preferred because it eliminates possible confounding factors, such as the taste of the solution or the delay between drug intake and the onset of the interoceptive effects that follow absorption. Indeed, the rapid rate of entry into the brain has been positively correlated with reports of 'high' in cocaine addicts (Volkow et al., 2000), and with the rate of operant responding in nonhuman primates and rats (Kato et al., 1987; Balster and Schuster, 1973; Panlilio et al., 1998). Interestingly, a rapid rate of i.v. infusion of cocaine has also been correlated with the rate that behavioral sensitization develops in rats (Samaha et al., 2002).

Widespread work on i.v. cocaine self-administration gave origin to several areas of research, including the study of factors related to the maintenance of drug taking, and to the investigation of pharmacological manipulations that could decrease drug taking. More importantly, the analysis of cocaine taking behavior in this paradigm gave ample contribution to the identification of neuropathways implicated in the reinforcing effects of cocaine in primates and in rats (for review, see Woolverton, 1992).

Compelling evidence that cocaine self-administration was dependent upon the increase of dopamine transmission

within the mesocorticolimbic system has built throughout the years of broad research. Studies generally based on intracerebral lesions (Roberts and Koob, 1982; Roberts et al., 1977, 1980), electrical brain stimulation (for review, see Wise, 1998), and pharmacological blockade (De Wit and Wise, 1977; Wilson and Schuster, 1972; Yokel and Wise, 1976; Bergman et al., 1990) widely support the implication of dopamine in cocaine-induced reinforcement. These studies first suggested that cocaine's ability to bind to the DAT and block uptake of dopamine within the mesocorticolimbic system was a major determinant for such effects. When Ritz et al. (1987a,b) reported, from a meta-analysis study, a high degree of correlation between the potency of cocaine-like drugs to act as inhibitors of dopamine reuptake and their potency to induce conditioned place preference or to maintain self-administration the DAT became accepted by the majority as cocaine's most prominent molecular target. However, because cocaine similarly binds to the SERT and the NET (Kuhar et al., 1991), the role of these pathways in mediating cocaine's reinforcing and rewarding effects could not be discarded. Indeed, several evidences support a major role of serotonergic pathways in the effects of cocaine (for review, see Walsh and Cunningham, 1997).

In spite of the extensive research on the topic, only the recent use of i.v. cocaine self-administration in mice provided the possibility to assess behavioral genetic questions through the use of transgenic technology (Rocha et al., 1997, 1998a). Even though interpretation of results obtained in KO mice may be limited by intrinsic developmental consequences that might occur due to the gene's deletion, the cocaine self-administration studies performed in different KO mice have overall highly expanded the knowledge on the brain circuitry and the molecular targets underlying cocaine reinforcing effects (Table 1, Stark et al., 1998).

Table 1
Summary of i.v. cocaine self-administration experiments reported in KO mice

Gene KO	i.v. cocaine self-administration	Reference
DAT	Maintained rate and dose response under FR	Rocha et al. (1998c)
NET	Dose response shifted to the right under FR	Rocha et al. (1999)
5-HT_{1B}	Maintained rate and dose response under FR, increased breakpoint under PR	Rocha et al. (1997, 1998a)
5-HT_{1A}	Dose response shifted to the left under FR	Rocha et al. (1998b)
5-HT_{2C}	Increased breakpoint under PR	Rocha et al. (2002)
NK1	Maintained rate under FR	Ripley et al. (2002)
TPA	Maintained rate under FR	Ripley et al. (1999)
DA D_2	Increased rate at low doses under FR	Caine et al. (2002)
Kir3/GIRK	Dose response downward shifted under FR	Morgan et al. (2003)
mGlur5	Abolished at 0.08–3.2 mg/kg/injection under FR	Chiamulera et al. (2001)
A_{2A}	Maintained under FR	Rocha et al. (2001)

FR = fixed ratio schedule; PR = progressive ratio schedule; DAT = dopamine transporter; NET = norepinephrine transporter; 5-HT = serotonin receptors1B, 1A and 2C; NK1 = receptor for substance P; tPA = tissue plasminogen activator; DA D_2 = dopamine D2 receptor; Kir3/GIRK = G protein-gated potassium channels; mGlur5 = metabotropic glutamate receptor 5; A_{2A} = adenosine 2A receptor.

3. Psychomotor and reinforcing effects of cocaine in DAT-KO mice

First described by Giros et al. (1996), the DAT-KO mouse attracted foremost interest particularly because of its accepted major role in mediating cocaine's reinforcing effects (Ritz et al., 1987a,b). A comprehensive research on these mice significantly clarified the cellular, neurochemical, and physiological role of the DAT in dopaminergic transmission, and gave rise to innovative concepts on the biology of the dopaminergic system (for review, see Gainetdinov and Caron, 2003). Most striking was evidence obtained from in vivo voltammetry studies in mouse striatal slices showing very high levels of extracellular dopamine (Jones et al., 1998) and very low clearance of dopamine. While single-pulse stimulation increased the extracellular dopamine lifetime in the mutants 300-fold, cocaine or amphetamine did not affect dopamine clearance (Giros et al., 1996). Meanwhile, depleted intracellular dopamine stores (Jones et al., 1998), and loss of function of dopamine D2 receptors (Jones et al., 1999) were similarly described and paradoxically characterized a dopamine-deficient neurotransmission in the mutants.

This hyperdopaminergic state was translated behaviorally as a pronounced locomotor hyperactivity and lower rate of habituation to novel environments (Sora et al., 1998; Gainetdinov et al., 1999; Mead et al., 2002a; Giros et al., 1996). Such hyperactivity appears to be sensitive only to treatments that decrease dopamine transmission. Inhibition of dopamine synthesis or blockade of dopamine receptors with haloperidol has been shown to decrease activity in the DAT-KO mouse (Spielewoy et al., 2000), while the effects of cocaine or amphetamine are controversial. Initial reports showed the DAT-KO mouse to be insensitive to these stimulants (Giros et al., 1996; Sora et al., 1998), but in others cocaine and amphetamine were reported to suppress the mutants activity (Gainetdinov et al., 1999; Spielewoy et al., 2001). One of the reasons of this discrepancy might be the high baseline activity of the DAT-KO mouse, which is often of a similar magnitude to the stimulant-induced hyperactivity in wild type control mice. It might be that differences in activity baseline confounded interpretation of the data, and eventually a high basal level of activity was masking any effects of drug in DAT-KO mice. In the attempt to offset this aspect, a recent study measured the behavioral effects of i.v. injected cocaine after the mice have fully adapted to the test environment, which occurred after 12 h (Mead et al., 2002a). Neither acute, nor repeated

injections of cocaine dose-dependently induced locomotor activation of the DAT-KO in this paradigm, confirming the early described insensitivity to the behavioral effects of cocaine in the absence of the DAT (Giros et al., 1996). Besides, cocaine did not induce behavioral sensitization in these mutants either.

Consequently, it was expected that cocaine would not be self-administered by DAT-KO mouse, which surprisingly was not the case (Rocha et al., 1998c). The mutants were able to acquire and to maintain i.v. cocaine self-administration as well as their wild type littermates, demonstrating that even in the absence of the DAT, the reinforcing effects of cocaine were preserved. A second study reported cocaine induced conditioned place-preference in these mutants (Sora et al., 1998) confirming that the motivational rewarding properties of cocaine were also preserved.

Taken together, these data clearly showed that in the absence of the DAT a dichotomy between the psychostimulant and reinforcing effects of cocaine occurred. While the absence of cocaine-induced locomotor activation suggested that the DAT was the major target for such effect, the maintenance of cocaine reinforcing effects suggested the opposite. In this case, the psychomotor stimulant theory (Wise and Bozarth, 1987) was not applicable, which further suggested that, under certain circumstances, psychostimulant and reinforcing effects of drugs are not mediated through similar mechanisms. Recently, a comparable dichotomy described between morphine-induced place preference and its locomotor effects in DAT-KO mice (Spielewoy et al., 2001) reaffirmed this assumption.

Cocaine self-administration in DAT-KO mice challenged the theory of DAT as the major target for cocaine's reinforcing effects (Caine, 1998; Uhl et al., 2002), and suggested that in the absence of DAT, cocaine interaction with other targets was efficient for assuring its reinforcing effects. Certainly, compensatory mechanisms due to the constitutional deletion of the DAT gene may occur, which limits the interpretation of the results to the specific DAT-KO mouse. For example, it might be that the hyperdopaminergic condition with down regulation of dopamine receptors described in the KO mouse had set the stage for other actions of cocaine to become prominent. Nonetheless, these results ultimately suggested that, in such circumstances, the reinforcing effects of cocaine were beyond the DAT, and cocaine interactions with the SERT and/or the NET were most likely to mediate such effects.

3.1. Alternative cocaine mechanism of action in DAT-KO mice—the 5-HT hypothesis

Several pieces of evidence suggest that cocaine blockade of 5-HT transmission is a major component of its reinforcing effects in DAT-KO mice. First, it was observed that while in wild type mice cocaine-induced Fos expression, as well as binding of the cocaine analog RTI-55 occurred in brain areas with major serotonergic and dopaminergic innervation, in the mutants these events only occurred in serotonergic areas (Rocha et al., 1998c). In addition, either cocaine or the 5-HT uptake blocker alaproclate completely displaced RTI-55 binding in the DAT-KO (Rocha et al., 1998c). In the same lines, a recent study showed cocaine-induced nuclear Fos protein expression in all the major central dopaminergic pathways in wild type mice, but only in selected limbic serotonergic areas implicated in stress and cognitive responses, such as the anterior olfactory nucleus, and the basolateral nucleus of the amygdala, in DAT-KO mice (Trinh et al., 2003).

However, a full elucidation of the exact contribution of 5-HT uptake blockade in DAT-KO mice is still missing. On one hand, the 5-HT uptake blocker fluoxetine was reported to decrease overall locomotion in the mutants (Gainetdinov et al., 1999). On the other, fluoxetine did not affect dopamine clearance in the nucleus accumbens of the mutant (Budygin et al., 2002), or dopamine uptake into synaptosomes from prefrontal cortex and striatum of wild type mice (Moron et al., 2002). A lack of effect of fluoxetine was equally observed when its systemic injection did not block cocaine self-administration in DAT-KO or wild type mice (Rocha, personal observation).

In light of this, the generation of a double DAT- and SERT-KO (DAT-KO/SERT-KO) mice (Sora et al., 2001) provided new insight into the relevance of the simultaneous role of these genes. While cocaine did induce conditioned place preference in each of the single KO strains (Sora et al., 1998), it did not in the double DAT-KO/SERT-KO mice (Sora et al., 2001). Developmental adaptations due to the double KO were more complex than the ones occurring after the KO of one single gene, but were not additional in nature. Of relevance was the significant reduction of expression of 5-HT1B receptors in the substantia nigra in the double mutants. Regardless the fact that it is unknown if these data can be extrapolated to wild type mice, they had the highest impact in cocaine induced reward. Albeit a negative result in the conditioned place preference paradigm does not completely discard the possibility that a motivational effect was present which was not recalled, results from this paradigm have in general paralleled results from drug self-administration (for review, see Bardo and Bevins, 2000). Therefore, absence of cocaine-induced place preference in the DAT-KO/SERT-KO mice would predict absence of cocaine-induced self-administration in these mutants, and emphasize a general hypothesis that cocaine modulation of dopamine transmission through 5-HT input is decisive for the expression of its reinforcing effects.

Studies of cocaine self-administration in different 5-HT receptor KO mice support this hypothesis, and further suggest that increased reinforcing efficacy of cocaine is ultimately correlated with increased dopamine tone, regardless of the underlying serotonergic mechanism. The KO of 5-HT1B receptors that are expressed in terminals of gamma-aminobutyric acid (GABA) interneurons in the nucleus accumbens, where they elicit inhibition of dopamine release,

were shown to be associated with higher cocaine reinforcing efficacy (Rocha et al., 1998a). Subsequently, in vivo microdialysis studies showed a significant increase in dopamine baseline in the nucleus accumbens of the mutants, suggesting that developmental adaptations occurred in the KO (Shippenberg et al., 2000). Cocaine-evoked additional dopamine release in these mutants supports a correlation between the increased dopaminergic tone and the reinforcing effects of cocaine. Correspondingly, the deletion of 5-HT2C receptors that are expressed in 5-HT post-synaptic terminals, was associated with higher release of dopamine in the nucleus accumbens and increased cocaine reinforcing efficacy (Rocha et al., 2002). In contrast to 5-HT1B-KO, in 5-HT2C-KO mice, baseline levels of dopamine in nucleus accumbens were comparable to wild type, suggesting that developmental adaptations due to the KO did not occur in this case. However, in both KO strains, cocaine higher reinforcing efficacy occurred along with higher nucleus accumbens dopamine. These results suggest that cocaine reinforcing efficacy did not depend on the specific mechanism underlying enhancement in dopaminergic transmission, but in the increase of dopamine at the end.

3.2. Alternative cocaine mechanism of action in DAT-KO mice—the norepinephrine hypothesis

NET is known to have a greater affinity for dopamine than the DAT itself (Giros et al., 1994). Therefore, in specific brain regions where DAT expression is significantly lower than NET, such as the prefrontal cortex (Moll et al., 2000), or in the absence of DAT as in the DAT-KO, it is conceivable that dopamine would be easily cleared through the NET, which would preserve neurotransmitter homeostasis. Overall evidence suggest that NET clearance of dopamine in the prefrontal cortex is implicated in cocaine reinforcing effects (Yamamoto and Novotney, 1998; Di Chiara et al., 1992; Tanda et al., 1997). In rats, cocaine maintains self-administration directly into the prefrontal cortex (Goeders and Smith, 1986), and systemic administration of the norepinephrine uptake inhibitor nisoxetine induces increase of extracellular dopamine in the prefrontal cortex (Snoddy and Tessel, 1985; Carboni et al., 1990).

In DAT-KO mice, the working hypothesis of dopamine clearance through NET was first explored in vitro, using synaptosomes prepared from striatum, prefrontal cortex and nucleus accumbens of DAT-KO, NET-KO and wild type control mice (Moron et al., 2002). Dopamine uptake was preserved in synaptosomes from the prefrontal cortex of DAT-KO, while it was disrupted in those of NET-KO mice. Additionally, cocaine, nisoxetine and the specific DAT blocker GBR 12909 differentially inhibited dopamine uptake into synaptosomes as a function of brain structure and genotype. Cocaine or nisoxetine significantly decreased dopamine uptake into synaptosomes from prefrontal cortex of wild type and DAT-KO mice, while GBR 12909 had no effect in any of the genotypes. Conversely, cocaine, nisoxetine or GBR 12909 inhibited dopamine uptake into synaptosomes from striatum of wild type and NET-KO mice, while they did not affect dopamine uptake into synaptosomes of DAT-KO mice. These results were in accordance with previous data showing the role of NET in removing dopamine from dopaminergic terminals in the prefrontal cortex (Di Chiara et al., 1992) in DAT-KO mice, reaffirming the relevance of this brain region in cocaine reinforcement.

Another brain region of interest is the medial part, or shell, of the nucleus accumbens, which has been implicated in modulation of drug reinforcement (Di Chiara and Imperato, 1988). Moderate to dense norepinephrine projections from the locus coerulus arrive in this region (Berridge et al., 1997) and provide the anatomical basis for a noradrenergic modulation. In vivo microdialysis studies described cocaine-induced increase of dopamine dialysate in the nucleus accumbens shell in DAT-KO and wild type mice (Carboni et al., 2001), further suggested that cocaine blockade of dopamine reuptake occurred through a DAT-independent mechanism in this region. Additionally, the NET inhibitor reboxetine enhanced nucleus accumbens dopamine only in DAT-KO mice (Carboni et al., 2001). However, this hypothesis was not supported by a recent study using in vivo voltammetry technique, where both cocaine and the NET inhibitor desipramine, failed to change dopamine clearance in the nucleus accumbens of DAT-KO mice (Budygin et al., 2002).

A consensus on how cocaine interferes with the release and uptake of dopamine in DAT-KO mice has not yet been reached, and therefore further studies are necessary. As discussed below, the generation of NET-KO mice (Xu et al., 2000) offered an additional tool to explore the actions of cocaine.

4. Psychomotor and reinforcing effects of cocaine in NET-KO mice

Neurochemical observations in NET-KO mice were analogous to the observations in DAT-KO mice. A prolonged synaptic lifetime of norepinephrine resulted in increase of extracellular concentration of norepinephrine, depletion of norepinephrine intraneuronal stores, and decreased α1-adrenoceptor binding in the hippocampus (Xu et al., 2000).

Behavioral evaluation of these mutants described them with decreased immobility in the tail suspension test, greater locomotor stimulation and conditioned place preference induced by cocaine (Xu et al., 2000). In the tail suspension test, in which antidepressants and psychostimulants are known to decrease immobility in mice (Porsolt et al., 1987), the norepinephrine and 5-HT uptake inhibitor desipramine, the 5-HT uptake inhibitor paroxetine or the dopamine reuptake inhibitor bupropion did not further increase activity in NET-KO mice (Xu et al., 2000). Likewise, repeated cocaine administration was initially described as not inducing behavioral sensitization in the mutants, which

led the authors to conclude that the NET-KO mouse was presensitized to cocaine (Xu et al., 2000).

However, more recently, a study investigating the stimulant effects of cocaine administered i.v. showed in part opposing results (Mead et al., 2002a). While, similarly to Xu et al., this study reported a decreased locomotor response to a novel environment in NET-KO mice, it showed opposite effects of cocaine. Acutely, cocaine dose-dependently induced lower motor activation in NET-KO in comparison to wild type control, but after repeated administration it induced a comparable increase in motor activation in both genotypes, characterizing similar development of behavioral sensitization in the mutants (Mead et al., 2002a). Because the two studies used mice that originated from the same source and were as well bred from heterozygous breeding pairs, it is unlikely that the differences observed were due to differences in the subjects themselves. On the other hand, the experimental conditions and, in particular, the route of cocaine administration differed entirely, with cocaine injected intraperitoneally (i.p.) in the study of Xu et al. It is possible that, in the mutants, under altered conditions of norepinephrine transmission (reduced clearance and increased extracellular concentration of norepinephrine in the striatum; Xu et al., 2000), the combination of cocaine with the stress of handling and injection (Ryabinin et al., 1999) interfered with the readout of the study. Conversely, when cocaine was injected under i.v. undetectable conditions (Mead et al., 2002b), it was possible to single out its motor-activating effects. Similar differences in the output of i.p. or i.v. administration of amphetamine in 5-HT_{1B}-KO mice have been reported (Bronsert et al., 2001), which reaffirm the relevance of the route of administration for studying the effects of psychostimulants in KO mice.

The progressive increase in response to cocaine after repeated i.v. administration (Mead et al., 2002a) that characterized comparable development of behavioral sensitization in wild type and NET-KO mice is also in contrast with previous findings (Xu et al., 2000). Besides the route of administration, it might be that the single dose of cocaine tested by Xu et al. was much higher than necessary to induce sensitization, which is characteristically dose-dependent (Post et al., 1988). Therefore, these results suggest that NET is not implicated in the development of behavioral sensitization to cocaine, but it probably plays a partial role in its acute effects.

This was confirmed by the report of cocaine self-administration in these mutants. NET-KO and wild type mice dose-dependently self-administered cocaine (0.25–4.0 mg/kg/infusion) (Rocha et al., 1999), but NET-KO mice did show a significant increase in their rate of cocaine self-administration, while their ED_{50} was approximately fourfold shifted to the right (wild type = 0.67 mg/kg, NET-KO = 2.6 mg/kg). Simultaneous record of motor activity and lever pressing during self-administration sessions showed that cocaine dose-dependently increased locomotor activity of wild type mice but not of NET-KO. Taken together, these results suggest that in the absence of the NET, a decrease in the psychostimulant and reinforcing potency of cocaine occurred. Apparently, these data are in contradiction with data obtained in the conditioned place preference paradigm where cocaine was reported to reverse the time spent in the non-preferred compartment in a much larger extent in the double NET-KO/SERT-KO mice when compared to wild type or to mice of any other combined genotype (i.e., NET-KO/SERT-WILD TYPE) (Hall et al., 2002). However, the interpretation of these data is difficult because first, an overall effect of NET genotype was not confirmed statistically, and second, a biased place preference paradigm was used. This accounts for one of the limitations of the conditioned place paradigm, when the animals prefer one of the compartments of the apparatus before any conditioning. Pairing the drug with the non-preferred compartment and showing the reversion of a previous aversive state does not necessarily mean to induce a true preference (Bardo and Bevins, 2000).

Overall, the alterations of the psychostimulant and reinforcing effects of cocaine in NET-KO mice support a partial norepinephrine mediation of such effects. Interestingly, several reports had implicated dysregulation of the norepinephrine system after cocaine exposure. In nonhuman primates, cocaine induced accumulation of norepinephrine in locus coerulus, amygdala and hippocampus (Madras and Kaufman, 1994), and in cocaine addicts during withdrawal the beta-blocker propranolol decreased scales for anxiety and depression (Kampman et al., 2001). Recently, it was reported that chronic cocaine self-administration in nonhuman primates decreased glucose metabolism and increased NET binding sites in the bed nucleus of the stria terminalis (Macey et al., 2003), which is part of the extended amygdala and a key site in the integration of stress and motivation (Delfs et al., 2000). The bed nucleus of the stria terminalis receives significant norepinephrine innervation, and send excitatory projections to the dopamine neurons in the ventral tegmental area where they can generate long-lasting alterations in the activity of dopamine neurons in vivo (Georges and Aston-Jones, 2001, 2002). It was hypothesized that reduction of brain activity and increased NET expression in the bed nucleus of the stria terminalis after chronic cocaine self-administration might have inhibited activation of dopamine neurons, thereby leading to perpetuation of drug taking as a mean to compensate such deficit (Macey et al., 2003). In light of these data, it is conceivable to similarly hypothesize that permanent increased noradrenergic tone in NET-KO mice equally dysregulated brain reward function.

5. Conclusion

The KO mouse technology represents and remains a powerful genetic tool for the study of addiction, in spite of its limitations. We revisited here studies of cocaine-

induced motor activation, behavioral sensitization and maintenance of i.v. self-administration in particular, in DAT-KO and NET-KO mice. While the exact mechanism(s) underlying such cocaine effects has not yet been fully determined, these studies brought together evidence that cocaine acts through diverse and not exclusive mechanisms. They shaped the notion that the reinforcing effects of cocaine are beyond the DAT, but not beyond dopamine.

The general concept that emerged from this research is that cocaine's actions at multiple sites are a dynamic process in which pathways may be exchangeable. In the KO mouse, when one pathway is eliminated, another pathway takes over. In humans, by analogy, it might be predictable that pathways would be individually shaped depending on the duration and profile of one's own drug-taking habit. The ideal therapeutic strategy would emphasize, besides the pharmacological approach, a customized design, which would take into account personal profile and context of drug taking.

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