The Discriminative Stimulus Properties of Hallucinogenic and Dissociative Anesthetic Drugs

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Abstract The subjective effects of drugs are related to the kinds of feelings they produce, such as euphoria or dysphoria. One of the methods that can be used to study these effects is the drug discrimination procedure. Many researchers have been trying to elucidate the mechanisms that underlie the discriminative stimulus properties of abused drugs (e.g., alcohol, psychostimulants, and opioids). Over the past two decades, patterns of drug abuse have changed, so that club/recreational drugs such as phencyclidine (PCP), 3,4-methylenedioxymethamphetamine (MDMA), ketamine, and cannabinoid, which induce perceptual distortions, like hallucinations, are now more commonly abused, especially in younger generations. In particular, the abuse of designer drugs, which aim to mimic the subjective effects of psychostimulants (e.g., MDMA or amphetamines), has been problematic. However, the mechanisms of the discriminative stimulus effects of hallucinogenic and dissociative anesthetic drugs are not yet fully clear. This chapter focuses on recent findings regarding hallucinogenic and dissociative anesthetic drug-induced discriminative stimulus properties in animals.

Keywords Discriminative stimulus properties • Hallucinogens • Psychedelics • Serotonin • Sigma-1 receptor

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1 Introduction

The most important determinant of a substance's abuse potential is the nature of the subjective effects that are produced by the drug's influence on the central nervous system. Alcohol, psychostimulants – like methamphetamine and cocaine – and opioids – such as morphine and heroin – produce a drug state that includes feelings referred to as euphoria. Hallucinogens and dissociative anesthetics have also been misused or abused mainly for recreational drugs. With regard to the relationship between drug-induced subjective effects and abuse potential, animal models have been developed to study the components of action of abused drugs that bear on their subjective effects in humans. One method that has considerable potential in this regard is the drug discrimination procedure, which has been used to study the mechanisms that underlie the discriminative stimulus properties of abused drugs, and the similarities among the discriminative stimulus properties of abused drugs.

Use of the club drugs 3,4-methylenedioxymethamphetamine (MDMA), including new psychoactive substances, lysergic acid diethylamide (LSD), became popular in the past few decades. Phencyclidine (PCP) and ketamine, which induce perceptual distortions (e.g., hallucinations, illusions) and disordered thinking (e.g., paranoia), are classified as dissociative anesthetic drugs. *Salvia divinorum* contains salvinorin A, which is a selective k-opioid receptor agonist and has dissociative effects, has been misused [1, 2]. On the other hand, it has been proposed that hallucinogenic effects mediated by sigma-1 receptors [3] are closely related to NMDA receptors or serotonin receptors [4, 5]. Even though these hallucinogenic drugs sometimes induce psychotomimetic effects, which are closely related to bad trips and dysphoria in humans, they have been abused for at least two decades. Interestingly, these hallucinogenic/psychedelic drugs induce both rewarding and aversive effects, depending on the details of conditioning as measured by conditioned place preference procedures in animals. While the discriminative stimulus properties of a hallucinogenic drug may be responsible for or be related to its rewarding or aversive effects, it is not yet clear exactly how the discriminative stimulus properties of hallucinogenic drugs influence for their reinforcing or aversive effects [6, 7].

Hallucinogenic drugs can be divided into distinct classes according to their chemical structures and pharmacological actions. Since the discriminative stimulus properties of a hallucinogenic drug are believed to be mediated by receptor mechanisms thought to be important for hallucinogenic effects, these drugs might substitute for the discriminative stimulus properties of other drugs (e.g., the non-hallucinogenic compound lisuride at least partially substitutes for the discriminative stimulus properties of LSD, which are mediated by the activation of

serotonergic 5-HT_{1A} and 5-HT_2 receptors) [8–10]. In most cases, each type of hallucinogenic drug exerts distinct discriminative stimulus properties. Thus, the discriminative stimulus properties of a hallucinogenic drug depend on its hallucinogenic effects and/or mechanisms of action. Several recent reports have provided new insight into the mechanisms of the discriminative stimulus properties of hallucinogenic drugs. The present chapter focuses on the mechanism(s) of the discriminative stimulus of hallucinogenic/psychotomimetic drugs. Furthermore, the possible relationship between the discriminative stimulus properties of hallucinogenic drugs and their reinforcing or aversive effects in animals was also investigated.

2 Discriminative Stimulus Effects of 5-HT-Related Compounds

MDMA and LSD (and related compounds, such as the hallucinogenic derivatives of phenethylamine and tryptamine) are known to regulate serotonergic systems to induce hallucinogenic effects. MDMA mainly releases serotonin from nerve terminals, and to a lesser extent dopamine, and, thereby, produces an enhanced mood with increased well-being or dysphoria and perceptual changes (in addition to hallucinations, illusions, and disordered thinking) in humans. Additionally, a history of MDMA use may influence the subsequent vulnerability to the use and abuse of MDMA in humans. In rodents, a large and growing body of evidence suggests that MDMA can induce hyperlocomotion and reinforcing/rewarding, aversive and discriminative stimulus properties [11].

The serotonin receptor superfamily consists of 14 subtypes that have been classified based on gene structure, amino acid sequence homology, and intracellular signaling cascades, and at least seven families of serotonin receptors (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_6, and 5-HT_7) have been identified. Serotonin 5-HT_2 and 5-HT_{1A} receptor agonists have opposite behavioral effects; however, activation of these receptors has a synergistic action on the locomotor activity induced by MDMA [12]. The synthetic tryptamine hallucinogen *N*,*N*-dipropyltryptamine partially to fully substitutes for the discriminative stimulus properties of hallucinogens like LSD, psilocybin, and MDMA, and LSD produces MDMA-like discriminative stimulus properties in rats [13], indicating that these 5-HT-related compounds show similar discriminative stimulus properties. 5-HT_{1A} receptor agonists exert MDMA-like discriminative stimulus properties; whereas, a 5-HT_{1A} receptor antagonist partially antagonizes the discriminative stimulus properties of MDMA in rats [14]. The activation of 5-HT_{1A} receptors elicits the stimulus properties of the tryptaminergic hallucinogen 5-MeO-DMT [15], indicating that the agonist actions of 5-HT_{1A} receptors play a role in the discriminative stimulus properties of serotonin-related hallucinogenic drugs. On the other hand, it has been clearly demonstrated that the activation of 5-HT_2 receptors plays a significant role in the

discriminative stimulus properties of LSD [15]. The discriminative stimulus properties of MDMA and LSD are more potently attenuated by 5-HT_2 receptor antagonists than by 5-HT_{1A} receptor antagonists in rats [7]. The perceptual changes, emotional excitation, and adverse responses induced by MDMA are reduced by 5-HT_2 receptor antagonists in humans [16]. A more recent study showed that serotonin 5-HT_2 receptors are crucial for the reinforcing effects induced by MDMA [17]. These results indicate that the activation of 5-HT_2 receptor is an essential element of the discriminative stimulus properties and subjective effects of serotonin-related hallucinogenic drugs, which are closely related to their reinforcing and/or aversive effects, and that a 5-HT_{1A}-mediated component may have facilitatory functions [7].

It is well known that psychostimulants increase not only dopamine levels in the synaptic cleft of the terminals of the dopaminergic system, but also serotonin and noradrenaline levels. In humans, both methamphetamine and MDMA induce an increase in wakefulness and euphoria [18, 19], and it is difficult to discriminate between them based on their subjective effects in humans [20]. Thus, MDMA and other psychostimulants generally produce similar subjective effects in humans. Previous animal studies have shown that while cocaine does not substitute for the discriminative stimulus properties of MDMA, MDMA substitutes for the discriminative stimulus properties of cocaine [21]. Amphetamine partially substitutes for the discriminative stimulus properties of MDMA [22]. In contrast, MDMA does not substitute for the discriminative stimulus properties of methamphetamine [7]. In cross-substitution tests, MDMA and methylphenidate do not cross-substitute for each other in rats that have been trained to discriminate between MDMA or methylphenidate and saline [7], indicating that the discriminative stimulus properties of MDMA are distinctly different from those of other psychostimulants in rats. As mentioned above, the serotonergic system plays an important role in the discriminative stimulus properties of MDMA. However, a high dose of MDMA increases the release of dopamine, and may substitute for the discriminative stimulus properties of psychostimulants. Interestingly, recent research may provide an answer. Amphetamine substitutes for the discriminative stimulus properties of MDMA in rats that have been trained to discriminate between a high dose, but not a low dose, of MDMA and saline [23]. The discriminative stimulus properties of MDMA depend on the training doses (dopamine vs. 5-HT); lower doses of MDMA enhance serotonin, whereas higher doses of MDMA is required to enhance the dopamine release. In the case of humans, high dose of MDMA was associated with more drug-related problems [24], MDMA is frequently taken in combination with other substances to boost its effects [25]. Therefore, subjective effects of MDMA in humans are mainly mediated by the activation of serotonergic systems in the case of regular use. On the other hand, MDMA increases “negative” mood; whereas, methamphetamine enhances only “positive” mood in humans [20]. In fact, activation of dopaminergic system is partly involved in the euphoric effects of MDMA in humans [26]. In contrast, MDMA-induced perceptual changes and emotional excitation are mediated by serotonergic system [27]. Thus, MDMA and other

psychostimulants, like methamphetamine, exert some overlapping and divergent effects. Particularly, serotonin-related subjective changes may explain why MDMA and other serotonin-related drugs are used recreationally.

3 Discriminative Stimulus Effects of PCP and k-Opioid Receptor Agonist

Ketamine and PCP, which are noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonists that induce a dissociative anesthetic effect, produce psychotomimetic effects, such as nightmares, hallucinations, and delusions. Noncompetitive NMDA receptor antagonists, such as PCP and MK-801, but not the noncompetitive NMDA receptor antagonist 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid, partially substituted for the discriminative stimulus properties of the barbiturate pentobarbital [28]; whereas, noncompetitive NMDA receptor antagonists, but not competitive NMDA receptor agonists, substituted for the selective k-opioid receptor agonist 2-(3,4-dichlorophenyl)-*N*-methyl-*N*-[(1R,2R)-2-pyrrolidin-1-ylcyclohexyl]acetamide (U-50,488H) [29]. These findings suggest that the discriminative stimulus properties of competitive and noncompetitive NMDA receptor antagonists are different from each other. Further, the spectrum of behaviors induced by competitive and noncompetitive NMDA-receptor antagonists is totally different: PCP and MK-801 induce potent hyperlocomotion with ataxia, which might be related to the induction of the psychotomimetic effects of these drugs [30], whereas competitive NMDA receptor antagonists induce sedation. Since PCP, like ketamine, is not selective for NMDA receptors (i.e., PCP and ketamine can regulate the dopaminergic and serotonergic systems and sigma-1 receptor function), it is likely that several components might be involved in the cue of the discriminative stimulus properties of NMDA receptor antagonist in animals; thus, representing a "compound" or "complex" discriminative cue.

k-opioid receptors are widely distributed in regions in the brain that are closely related to rewarding effects, aversive effects, mood and cognitive functions, such as the ventral tegmental area, substantia nigra, nucleus accumbens, striatum, amygdala, locus coeruleus, hypothalamus, and dorsal raphe nucleus in human and rat brains, and are also located in the spinal cord and peripheral tissues [28], which suggests that k-opioid receptor ligands may regulate many functions in the brain. Previous studies have shown that k-opioid receptor agonists exert antinociceptive effects without producing robust reinforcing or rewarding effects. Further, k-opioid receptor agonists exert antinociceptive effects without producing robust reinforcing/rewarding effects. On the other hand, the k-opioid receptor agonist spiradoline causes sedation and dysphoria but no euphoria [31], whereas enadoline induces feelings of depersonalization in humans [32]. Furthermore, Salvinorin A also produces strong dissociative effects and memory impairment, which only partially overlap with classic hallucinogen effects [1]. Therefore, k-opioid receptor

agonists produce hallucinogenic effects and dysphoria [31, 29]. Most k-opioid receptor agonists, including salvinorin A, but not the μ-opioid receptor agonists morphine or fentanyl or the δ-opioid receptor agonist SNC80, can substitute for the discriminative stimulus properties of the prototypic k-opioid receptor agonists U50,488H and U69593 [29, 33, 34]. These previous findings indicate that the cue of the discriminative stimulus properties of k-opioid receptor agonists is not shared by the discriminative stimulus properties of other opioid receptor agonists, and closely linked to dysphoric (aversive) effects.

PCP and MK-801 substitute for the discriminative stimulus properties of U50,488H [29]. Furthermore, the discriminative stimulus properties of U50,488H, the substitution of PCP for the discriminative stimulus properties of U50,488H, and the discriminative stimulus properties of ketamine were significantly blocked by the sigma-1 receptor antagonist NE-100 ([35, 36]; for an overview of sigma-1 receptors, see next section). On the other hand, sigma-1 receptor agonists such as (+)-pentazocine and SKF10,047 completely substituted for the discriminative stimulus properties of U50,488H [35], indicating that the discriminative stimulus properties of k-opioid receptor agonists and the k-opioid receptor agonist-like discriminative stimulus properties of noncompetitive NMDA receptor antagonists are at least in part mediated by sigma-1 receptors. It should be noted here that partial substitution of fluvoxamine, which has sigma-1 receptor agonistic action [37], for the discriminative stimulus properties of MDMA was completely suppressed by NE-100. Thus, a sigma-1 receptor agonist, k-opioid receptor agonist, and noncompetitive NMDA receptor antagonist-related cue may be related to psychotomimetic-like discriminative stimulus properties.

4 Hallucination and Sigma-1 Receptors

The sigma-1 receptor agonist SKF10,047 produces hallucinogenic/psychotomimetic effects. U50,488H-induced aversive effects, which are related to its psychotomimetic potential, are completely suppressed by sigma-1 receptor antagonist [35]. Further, it was believed that the hallucinogenic effects of PCP were mediated by sigma-1 receptors. Sigma-1 receptors are specifically localized at the interface between endoplasmic reticulum (ER) and mitochondria, the so-called mitochondria-associated ER membrane (MAM) inside the ER, and regulate Ca^{2+} signaling by stabilizing 1,4,5-triphosphate (IP_3) receptors as an ER chaperone protein [38]. The activity of sigma-1 receptors could be reciprocally inhibited by an association with binding immunoglobulin protein (BiP) through the formation of a sigma-1 receptor-BiP complex. Sigma-1 receptor agonists binding to sigma-1 receptors could exhibit chaperone activity by breaking the tether of the sigma-1 receptor-BiP complex [39], and enhance the Ca^{2+} through IP_3 receptors [40]. On the other hand, a sigma-1 receptor agonist may cause a translocation of sigma-1 receptor from the MAM to the plasma membrane where the sigma-1 receptor may bind to receptors (D_1 or NMDA-receptor) or ion channels (e.g., Kv1.2 channel)

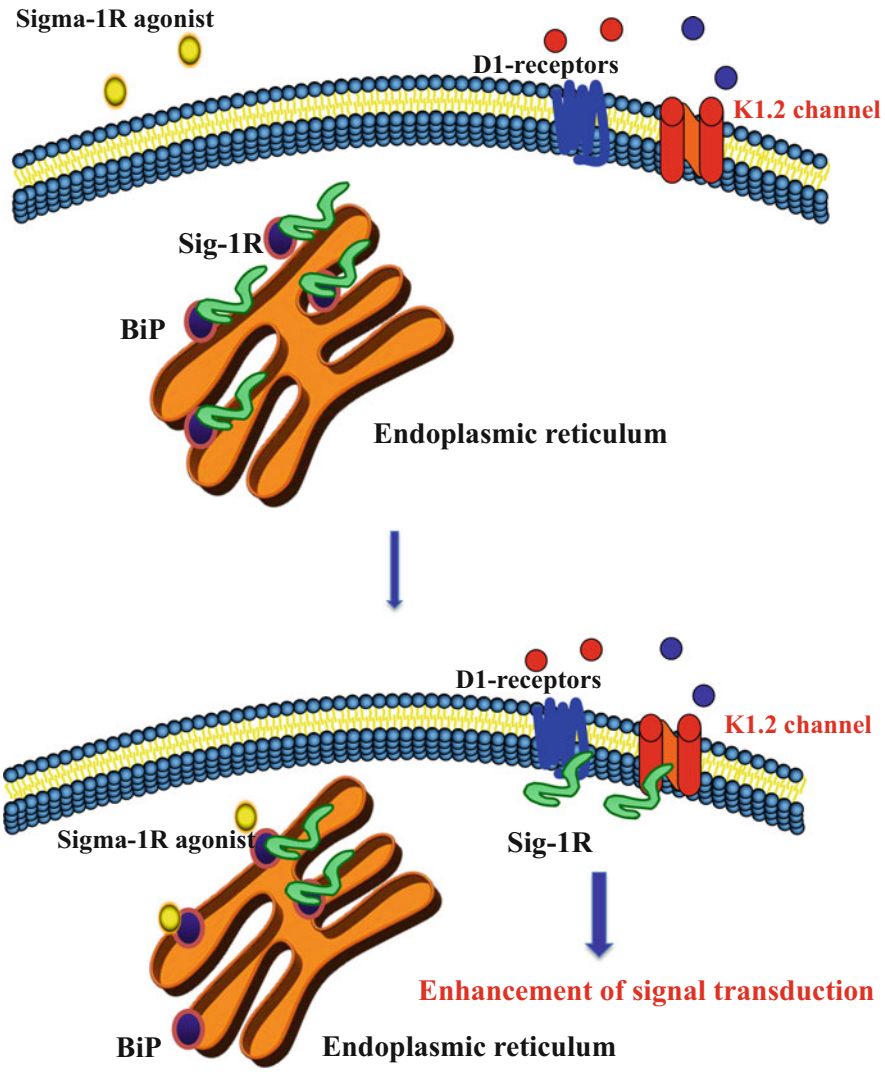

Fig. 1 Hypothetical scheme illustrating the regulation of signaling mediated by sigma-1 receptors. Sigma-1 receptors at the mitochondrion-associated endoplasmic reticulum (ER) function as ligand-activated molecular chaperones. Sig-1R agonists cause the dissociation of Sig-1Rs from another ER chaperone, binding immunoglobulin protein (BiP), allowing translocation of Sig-1Rs from ER to G-protein couples receptors and/or channels to regulate their signal transduction

that are regulating the signaling [41–43]. Recently, the endogenous hallucinogenic amine *N*,*N*-dimethyltryptamine (DMT) was shown to be an endogenous sigma-1 receptor ligand, and DMT and sigma-1 receptor agonists were shown to induce the dissociation of sigma-1 receptors from the sigma-1 receptor-BiP complex [3]. As noted above, the sigma-1 receptor antagonist NE-100 significantly attenuated the

discriminative stimulus properties of U-50,488H and the U-50,488H-like discriminative effects of PCP. However, the mechanism that underlies the involvement of sigma-1 receptors in the discriminative stimulus properties of U50,488H and the U50,488H-like discriminative stimulus properties of PCP remains unclear. One possibility is that k-opioid receptor agonists [34] as well as PCP [44] can activate extracellular signal-regulated kinase (ERK), and this activation of ERK induces the up-regulation of sigma-1 receptors [45]. Sigma-1 receptors translocated from the ER to the cellular membrane by sigma-1 receptor agonists negatively or positively regulate Src kinase, dopamine D_1 receptors, neurotropic tyrosine kinase receptor type 2 (TrkB), NMDA receptors, and $Kv_{1.2}$ channels [43, 46] (see Fig. 1). Such intracellular events might be involved in the psychotomimetic-like discriminative stimulus properties. Taken together, these results suggest that k-opioid receptor agonists and noncompetitive NMDA receptor antagonists may regulate endogenous sigma-1 receptor systems by regulating DMT, which induces a hallucinogenic effect. Therefore, the release of DMT by k-opioid receptor agonists and noncompetitive NMDA receptor antagonists should be addressed in future research.

5 Conclusion

Serotonin-related compounds and noncompetitive NMDA receptor antagonists/k-opioid receptor agonists induce hallucinations in humans and discriminative properties and reinforcing and aversive effects in animals. Previous studies have indicated that the activation of 5-HT_2 receptors plays a role in the discriminative stimulus properties of U50,488H, PCP, MDMA, and LSD in animals [15, 47]. Even though these hallucinogenic drugs induce similar behavioral phenotypes in some cases, each type of drug exerts different discriminative stimulus properties by regulating different receptors and signals. LSD and MDMA do not substitute for the discriminative stimulus properties of PCP in rats [15]. The discriminative stimulus properties of PCP were diminished by combination with LSD or MDMA in rats, presumably due to masking effects. A recent study showed that MDMA can regulate the endogenous k-opioid system mediated by the activation of 5-HT_2 receptors [48]. Therefore, it is possible that the hallucinogenic effects of U50,488H, PCP, MDMA, and LSD are mediated, at least in part, through the activation of 5-HT_2 receptors followed by sigma-1 receptors. While these drugs share some similarities in their mechanism of action, they differ with regard to the cue of their discriminative stimulus properties. On the other hand, tetrahydrocannabinol induced more robust cognitive impairment than MDMA, and their co-administration did not exacerbate the effects of either drug alone on cognitive function. However, the co-administration of tetrahydrocannabinol with MDMA increased subjective drug effects and drug strength compared with MDMA alone, which may explain the widespread use of this combination [49]. MDMA did not induce cannabinoid-like discriminative stimulus properties in rats [50]. These results suggest that cannabinoid receptor agonist has distinct discriminative

stimulus properties compared to its serotonergic-related effects. It should be noted here that humans can recognize hallucinogenic as a subjective effects induced by drugs. Nobody knows that animals could recognize whether they are having a hallucination or hallucinogenic drug-induced discriminative stimulus properties are related to hallucinogenic state, however, hallucinogenic and dissociative anesthetic drugs induce abnormal behaviors (e.g., head weaving, head-twitching, and ataxia). Furthermore, little is known about the specific regions that may part in the discriminative stimulus effects of hallucinogenic and dissociative anesthetic drugs. Such future findings may give us a better understanding of the underlying mechanisms of the discriminative stimulus effects of hallucinogenic and dissociative anesthetic drugs.

In conclusion, most hallucinogenic/psychotomimetic drugs induce distinct discriminative stimulus properties in animals, which may be related to their reinforcing or aversive effects. It is well known that most hallucinogenic drugs induce euphoria as well as dysphoria in humans depending on the situation. Thus, the discriminative stimulus properties of hallucinogens provide a reliable tool for investigating the subjective effects in humans. The discriminative stimulus properties of hallucinogenic drugs can be classified based on the underlying mechanism by which they exert their effects, such as whether they are mediated by 5-HT_2/sigma-1 (even though these receptors might be cross-linked). Based on previous results, the mechanisms of the discriminative stimulus properties of hallucinogenic drugs are related, at least partially, to their aversive effects. Interestingly, we recently interviewed 10 ex-polydrug abusers who were undergoing rehabilitation and asked them about the difference between the subjective effects of methamphetamine and hallucinogens, such as MDMA and cannabinoid. All of them stated that the subjective effects of MDMA and cannabinoid are totally different from those of methamphetamine, and there is no relapse for MDMA or cannabinoid, unlike in the case of methamphetamine. It is unclear how hallucinogenic effects may induce aversive and reinforcing effects accompanied by subjective effects/discriminative stimulus. MDMA was not a potent reinforcer in a self-administration study [6]; the ex-polydrug abusers mentioned above stated that they just enjoy the hallucination. Further research should address these points.

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