**Current Perspective**

**Discriminative Stimulus Effects of Hallucinogenic Drugs: a Possible Relation to Reinforcing and Aversive Effects**

Tomohisa Mori¹, Kazumi Yoshizawa¹, Masahiro Shibasaki¹, and Tsutomu Suzuki¹,*

¹Department of Toxicology, Hoshi University School of Pharmacy and Pharmaceutical Sciences, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan

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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 are trying to elucidate the mechanisms that underlie the discriminative stimulus effects of abused drugs (e.g., alcohol, psychostimulants, and opioids). Over the past two decades, the patterns of drug abuse have changed, so that club/recreational drugs such as phencyclidine (PCP), 3,4-methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), and ketamine, which induce perceptual distortions, like hallucinations, are now more commonly abused, especially in younger generations. However, the mechanisms of the discriminative stimulus effects of hallucinogenic drugs are not yet fully clear. This review will briefly focus on the recent findings regarding hallucinogenic/psychotomimetic drug-induced discriminative stimulus effects in animals. In summary, recent research has demonstrated that there are at least two plausible mechanisms that can explain the cue of the discriminative stimulus effects of hallucinogenic drugs; one is mediated mainly by 5-HT₂ receptors, and the other is mediated through sigma-1 (σ₁)-receptor chaperone regulated by endogenous hallucinogenic ligand.

**Keywords:** discriminative stimulus effect, hallucinogen, serotonin, sigma-1 (σ₁) receptor

**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 syndrome that includes feelings referred to as euphoria. 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. With the drug discrimination procedure, especially in studies on the discriminative stimulus effects of abused drugs, the mechanisms that underlie the discriminative stimulus effects of abused drugs and the similarities among the discriminative stimulus effects of abused drugs have been studied. A growing of body evidence obtained from several behavioral pharmacological techniques (e.g., self-administration, conditioned place preference, microdialysis, and drug discrimination procedure) has demonstrated that the dopaminergic, especially the mesolimbic, system plays a crucial role in the discriminative, reinforcing and rewarding effects of abused drugs.

Use of the club drugs 3,4-methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), phencyclidine (PCP), and ketamine, which induce perceptual distortions, like hallucinations, illusions, and disordered thinking such as paranoia, at parties became popular in the 1990s. Salvia divinorum and cannabis contain salvinorin A and cannabinoids, respectively, which have hallucinogenic effects. 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/psychotomimetic drugs induce both rewarding and aversive effects, depending on the details of conditioning as measured by conditioned place preference procedures in animals. The cue of the discriminative stimulus effects of a hallucinogenic drug may trigger its rewarding or aversive effects in animals. However, it is not yet clear how the discriminative stimulus effects of these hallucinogenic drugs significantly contribute to their reinforcing or aversive effects.

Hallucinogenic drugs can be divided into distinct classes according to their chemical structures and pharmacological action. Since the discriminative stimulus effects of a hallucinogenic drug are related to its hallucinogenic effect, these drugs might generalize to the discriminative stimulus effects of other drugs, and the non-hallucinogenic compound lisuride at least partially generalize to the discriminative stimulus effects of other drugs, and the non-hallucinogenic compound lisuride at least partially generalize to the discriminative stimulus effects of LSD, psilocybin, and MDMA; and LSD produces MDMA-like discriminative stimulus effects in rats (5), indicating that these 5-HT-related compounds show similar discriminative stimulus effects. 5-HT1A-receptor agonists have MDMA-like discriminative stimulus effects, whereas a 5-HT1A-receptor antagonist could partially antagonize the discriminative stimulus effects of MDMA in rats (6). The activation of 5-HT1A receptors elicits the stimulus effects of the tryptamnergic hallucinogen 5-MeO-DMT (7), indicating that the agonistic actions of 5-HT1A receptors play a role in the discriminative stimulus effects of 5-HT-related hallucinogenic drugs. On the other hand, it has been clearly demonstrated that the activation of 5-HT1 receptors plays a significant role in the discriminative stimulus effects of LSD (7). The discriminative stimulus effects of MDMA and LSD are more potently attenuated by a 5-HT2-receptor antagonist than by a 5-HT1A-receptor antagonist in rats. A more recent study showed that 5-HT2 receptors are crucial for the reinforcing effects induced by MDMA (8). The perceptual changes, emotional excitation, and adverse responses induced by MDMA are reduced by 5-HT2-receptor antagonists in humans. While 5-HT2- and 5-HT1A-receptor agonists have opposite behavioral effects, activation of these receptors has synergistic action on the locomotor activity induced by MDMA (9). These results indicate that the activation of 5-HT2 receptors is an essential element of the discriminative stimulus and subjective effects of 5-HT-related hallucinogenic drugs, which are closely related to their reinforcing and/or aversive effects, and that a 5-HT1A-mediated component may have facilitatory functions.

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 the 5-HTnergic systems to induce hallucinogenic effects. MDMA mainly releases 5-HT 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 effects (4). The 5-HT-receptor superfamiliy consists of 14 subtypes that have been classified based on gene structure, amino acid se-quence homology, and intracellular signaling cascades, and at least seven families of 5-HT receptors (5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT6, and 5-HT7) have been identified. The synthetic tryptamine hallucinogen N,N-dipropyltryptamine partially to fully generalizes to the discriminative stimulus effects of hallucinogens like LSD, psilocybin, and MDMA; and LSD produces MDMA-like discriminative stimulus effects in rats (5), indicating that these 5-HT-related compounds show similar discriminative stimulus effects. 5-HT1A-receptor agonists have MDMA-like discriminative stimulus effects, whereas a 5-HT1A-receptor antagonist could partially antagonize the discriminative stimulus effects of MDMA in rats (6). The activation of 5-HT1A receptors elicits the stimulus effects of the tryptamnergic hallucinogen 5-MeO-DMT (7), indicating that the agonistic actions of 5-HT1A receptors play a role in the discriminative stimulus effects of 5-HT-related hallucinogenic drugs. On the other hand, it has been clearly demonstrated that the activation of 5-HT1 receptors plays a significant role in the discriminative stimulus effects of LSD (7). The discriminative stimulus effects of MDMA and LSD are more potently attenuated by a 5-HT2-receptor antagonist than by a 5-HT1A-receptor antagonist in rats. A more recent study showed that 5-HT2 receptors are crucial for the reinforcing effects induced by MDMA (8). The perceptual changes, emotional excitation, and adverse responses induced by MDMA are reduced by 5-HT2-receptor antagonists in humans. While 5-HT2- and 5-HT1A-receptor agonists have opposite behavioral effects, activation of these receptors has synergistic action on the locomotor activity induced by MDMA (9). These results indicate that the activation of 5-HT2 receptors is an essential element of the discriminative stimulus and subjective effects of 5-HT-related hallucinogenic drugs, which are closely related to their reinforcing and/or aversive effects, and that a 5-HT1A-mediated component may have facilitatory functions.

3. Discriminative stimulus effects of PCP and κ-opioid receptor agonist

Ketamine and PCP, which are non-competitive NMDA-receptor antagonists that induce a dissociative anesthetic effect, produce psychotomimetic effects such as nightmares, hallucination, and delusion. Competitive NMDA-receptor antagonists, but not non-competitive NMDA-receptor antagonists, generalized to the discriminative stimulus effects of pentobarbital (10), whereas non-competitive NMDA-receptor antagonists, but not competitive NMDA-receptor agonists, generalized to those of U-50,488H (11). These findings suggest that the cues of the discriminative stimulus effects of competitive and non-competitive NMDA-receptor antagonists are different from each other. Further, the phenotype of be-
haviors induced by competitive and non-competitive 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 (12), 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 (σ1)-receptor function], it is likely that several components might be involved in the cue of the discriminative stimulus effects of NMDA-receptor antagonist in animals.

κ-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 (13), which indicates that κ-opioid ligands may regulate many functions in the brain. Previous studies have shown that κ-opioid receptor agonists exert anatoxicceptive effects without producing robust reinforcing as well as rewarding effects. κ-Opioid receptor agonists exert antinociceptive effects without producing robust reinforcing/rewarding effects. Most κ-opioid receptor agonists, including salvinorin A, but not the μ-opioid receptor agonists morphine and fentanyl or the δ-opioid receptor agonist SNC80, can generalize to the discriminative stimulus effects of the prototypic κ-opioid receptor agonists U50,488H and U69593 (11, 14, 15), indicating that the cue of the discriminative stimulus effects of κ-opioid receptor agonists is not shared by the discriminative stimulus effects of other opioid receptor agonists. Nevertheless, PCP and MK-801 generalize to the discriminative stimulus effects of U50,488H. Furthermore, the discriminative stimulus effects of U50,488H, U50,488H-like discriminative stimulus effects of PCP, and discriminative stimulus effects of ketamine were significantly attenuated by the σ1-receptor antagonist NE-100 (16, 17). On the other hand, σ1-receptor agonists such as (+)-pentazocine and SKF10,047 completely generalized to the discriminative stimulus effects of U50,488H (16), indicating that the discriminative stimulus effects of κ-opioid receptor agonists and the κ-opioid receptor agonist–like discriminative stimulus effects of non-competitive NMDA-receptor antagonists are at least in part mediated by σ1 receptors.

4. Hallucination and σ1 receptors

The σ1 receptor was originally thought to be a type of opioid receptor, and the σ1-receptor agonist SKF10,047 produces hallucinogenic/psychotomimetic effects. U50,488H-induced aversive effects, which are related to its psychotomimetic potential, are completely suppressed by a σ1-receptor antagonist (16). Further, it was believed that the hallucinogenic effects of PCP were mediated by σ1 receptors. Recently, the functions and localization of σ1 receptors have been unveiled (18). σ1-Receptors are specifically localized at the interface between the endoplasmic reticulum (ER) and mitochondria, the so-called mitochondria-associated ER membrane (MAM) inside the ER, and regulate Ca2+ signaling by stabilizing 1,4,5-triphosphate receptors as an ER chaperone protein (18). As noted above, the σ1-receptor antagonist NE-100 significantly attenuated the discriminative stimulus effects of U-50,488H and the U-50,488H-like discriminative effects of PCP. However, the mechanism that underlies the involvement of σ1 receptors in the discriminative stimulus effects of U50,488H and the U50,488H-like discriminative stimulus effects of PCP remains unclear. One possibility is that a κ-opioid receptor agonist (15, 19) as well as PCP (20) can activate extracellular signal–regulated kinase (ERK), and this activation of ERK induces the up-regulation of σ1 receptors (21). The activity of σ1 receptors could be reciprocally inhibited by an association with binding immunoglobulin protein (BiP) through the formation of a σ1 receptor–BiP complex, and σ1-receptor agonists could exert a chaperone activity with respect to σ1 receptors by breaking the tether of the σ1 receptor–BiP complex (18). Recently, the endogenous hallucinogenic amine N,N-dimethyltryptamine (DMT) was shown to be an endogenous σ1-receptor ligand, and DMT as well as σ1-receptor agonists were shown to induce the dissociation of σ1 receptors from the σ1 receptor–BiP complex (22). Taken together, these results suggest that κ-opioid receptor agonists and non-competitive NMDA-receptor antagonists may regulate endogenous σ1-receptor systems by regulating DMT, which induces a hallucinogenic effect. Therefore, the release of DMT by κ-opioid receptor agonists and non-competitive NMDA-receptor antagonists should be addressed in future research.

5. Discriminative stimulus effects of cannabinoids

Marijuana is the most commonly used illegal drug in the United States. It has been well recognized that Cannabis sativa (marijuana) has abuse potential in humans (even it has dysphoric effect), although the pharmacological mechanism by which its psychoactive ingredient, Δ9-tetrahydrocannabinol (THC), exerts reinforcing or rewarding effects is not yet clear. There are at least two major cannabinoid receptors (CB1 and CB2 receptors); CB1 receptors are mainly localized throughout the brain...
and have been proposed to form a heterodimer with D₂ or orexin-1 receptors. On the other hand, CB₂ was identified as a peripheral receptor that is expressed in macrophages, although some are found in microglial cells (23). Marijuana produces changes in mood and perception and sometimes induces unpleasant reactions such as panic or hallucination in humans. In animals, the rewarding and aversive effects of cannabinoid receptor agonists are known to depend on the situation (e.g., age, dose, number of conditioning trials, injection-to-placement intervals, and pre-training drug exposure), and the activation of adrenergic receptors, especially the β₁-adrenergic receptor in the nucleus accumbens, might be involved in the aversive effects of cannabinoid receptor agonists (24). However, little is known about the mechanism that underlies the cue of the discriminative stimulus effects of THC (e.g., the activation of CB₁ receptors is required to generalize to the discriminative stimulus effects of THC in animals that have been trained to discriminate between THC and vehicle, indicating that the activation of CB₁ receptors plays an important role in the discriminative stimulus effects of THC).

Cannabinoids and μ-opioid receptor agonists exert similar behavioral effects in rats, such as antinociceptive effects, sedation, and rewarding effects. In humans, THC, like morphine, induces reinforcing effects and hallucinations. Therefore, some investigators have recently been focusing on the interactions between cannabinoid and opioid systems in the brain. μ-Opioid and cannabinoid receptors are co-distributed in the area of the dorsal horn of the spinal cord and areas of the brain that control antinociceptive effects, such as the periaqueductal gray, raphe nuclei, and central medial thalamic nuclei (25). Biological and molecular biological findings suggest that cannabinoid receptors form heterodimers with μ-opioid receptors (26). Several behavioral effects that are induced by cannabinoid receptor agonists have been shown to at least partially depend on the activation of endogenous opioid systems, indicating that there is cross-talk between endogenous cannabinoid and opioid systems (27); the opioid receptor antagonist naltrexone could attenuate the discriminative stimulus effects of THC (28), suggesting that the endogenous opioid system is involved in the discriminative stimulus effects of THC. However, animal studies have shown conflicting findings. For example, cannabinoid receptor agonists enhance the antinociceptive effects and hyperlocomotion induced by morphine in rodents (25). The discriminative stimulus effects of THC could be attenuated by μ-opioid receptor agonists (29). Further, cannabinoid receptor agonist abolished the rewarding effects of morphine (30). Regarding these discrepant results, μ-opioid or cannabinoid receptors activate mitogen-activated protein kinase (MAPK), which is important for acquisition of the reward process. These MAPK-activating effects of a μ-opioid receptor agonist and a cannabinoid receptor agonist reciprocally abolish each other when these agonists are combined (31). Thus, cannabinoid receptor agonists could differentially alter the behavioral effects induced by morphine depending on the conditions.

With regard to the interaction between the discriminative stimulus effects of cannabinoid and μ-opioid receptor agonists, it should be noted that the mechanism of the discriminative stimulus effects of morphine is different from that of the morphine-induced rewarding effects in rats (32). Morphine-induced rewarding effects are mediated by μ₂-opioid receptors, followed by activation of the dopaminergic system, while the discriminative stimulus effects of morphine are not affected by dopamine-receptor antagonists and are completely attenuated by a μ₁-opioid receptor antagonist. Furthermore, it has been reported that dopamine D₂–receptor mechanisms may not play a major role in mediating the psychotomimetic and perception-altering effects of THC in humans (33). Thus, some effect other than a reinforcing effect, such as an antinociceptive-related or hallucinogenic effect, which is not mediated by activation of the dopaminergic system, plays a role in the discriminative stimulus effects of THC. On the other hand, there is cross-talk between the endocannabinoid system and k-opioid receptor system. In fact, THC-induced aversive effects were abolished in k-opioid receptor–knockout mice (27), whereas a cannabinoid receptor agonist, but not MDMA, partially generalized to the discriminative stimulus effects of a k-opioid receptor agonist (T. Mori et al., unpublished observation). Thus, it is likely that the discriminative stimulus effects of THC may reflect their aversive effects in animals. Therefore, further studies are needed to elucidate both the roles that opioid systems play in the discriminative stimulus effects of THC and the relation between the discriminative stimulus and aversive effects of THC.

6. Conclusion

Cannabinoid receptor agonists, 5-HT-related compounds, and non-competitive NMDA-receptor antagonists / κ-opioid receptor agonists induce hallucinations in humans and discriminative stimulus, reinforcing, and aversive effects in animals. Previous studies have indicated that the activation of 5-HT₂ receptors plays a role in the discriminative stimulus effects of U50,488H, PCP, MDMA, and LSD in animals (7, 34). Even though these hallucinogenic drugs in some cases induce similar behavioral phenotypes, each type of drug exerts different discriminative stimulus effects by regulating different receptors and signals (Fig. 1). LSD and MDMA do not
generalize to the discriminative stimulus effects of PCP in rats (7). The discriminative stimulus effects of PCP were diminished by combination with LSD or MDMA in rats, presumably due to masking effects (7). A recent study showed that MDMA can regulate the endogenous κ-opioid system mediated by the activation of 5-HT2 receptors (35). 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-HT2 receptors. While these drugs share some similarities in their mechanism of action, they differ with regard to the cue of their discriminative stimulus effects. On the other hand, THC 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 THC with MDMA increased subjective drug effects and drug strength compared with MDMA alone, which may explain the widespread use of this combination (36). MDMA did not induce cannabinoid-like discriminative stimulus effects in rats (37). These results suggest that a cannabinoid receptor agonist has distinct discriminative stimulus effects compared to its 5-HT-related effects.

In conclusion, most hallucinogenic/psychotomimetic drugs induce distinct discriminative stimulus effects 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 effects of hallucinogen provide a reliable tool for investigating the subjective effects in humans. The discriminative stimulus effects of hallucinogenic drugs can be classified based on the underlying mechanism by which they exert their effects, such as whether they are mediated by σ₁, 5-HT₂, or CB₁ receptors (even though these receptors might be cross-linked). Based on previous results, the mechanisms of the discriminative stimulus effects of hallucinogenic drugs are related to their aversive effects. Therefore, it is unclear how hallucinogenic effects may induce aversive effects and how the discriminative stimulus effects of hallucinogenic drugs induce aversive effects.

References


