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Insights into Psychoactive Drug Effects: The Role of Drug Discrimination Techniques

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Abstract

Psychoactive drugs exert profound effects on the central nervous system, influencing behavior and perception. Understanding these effects is crucial for both scientific research and clinical practice. This article provides an overview of the application of drug discrimination techniques in studying the subjective effects, pharmacological mechanisms, individual differences, and drug classification of psychoactive substances. Through drug discrimination models, researchers gain insights into the pharmacological specificity and predictive validity of these substances, particularly hallucinogens such as LSD and cannabinoids like THC. The article highlights the contributions of drug discrimination techniques in elucidating the pharmacological actions of psychoactive drugs, offering opportunities for further exploration into their therapeutic potential and abuse-related properties.

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1. Introduction

Drug abuse has become a significant public health issue in today's society on a global scale. Drug abuse refers to the repetitive and excessive use of a substance for non-medical purposes to pursue its specific psychoactive effects, including sedation, euphoria, hallucination, impulsivity, as well as alterations in cognition and emotion [1][2][3]. The abuse potential of drugs is largely influenced by their subjective sensitivity; therefore, laboratories often establish animal models through

drug discrimination procedures to study the subjective effects of abused drugs [4][5][6].

Drug discrimination technique is a behavioral pharmacological method used to determine whether a drug possesses discriminative stimulus properties in controlling behavior, reflecting its subjective effects [7][8][9]. It assesses whether an organism can discriminate or differentiate between two or more drugs, leading to distinct behavioral responses. This method, primarily based on observing the subjective experiences of drugs, exhibits strong selectivity in pharmacology, reflecting the relative importance and distribution of corresponding receptors in the body, and is considered one of the primary methods for evaluating drug abuse liability. Currently, drug discrimination technique is widely employed in preclinical drug development for central nervous system drugs, particularly in research concerning the psychopharmacology of abused drugs.

2. Overview of Drug Discrimination Technique

2.1. Characteristics of Drug Discriminative Stimuli

Drug discrimination technique primarily investigates the discriminative stimulus properties of drugs. Stimulus, in its basic definition, refers to any factor that influences an organism's response by eliciting a reaction. In experiments, stimuli traditionally refer to environmental factors such as tones, lights, foot shocks, etc., typically established to assess changes in organismic responses when stimuli vary [10][11][12]. A stimulus is usually defined by its characteristics or attributes. Clearly, drugs can also act as stimuli affecting organismic behavior and functional responses. The biological actions of drug stimuli on the central nervous system mediate their stimulus characteristics. Drug discrimination control represents the behavioral relationship between environmental events (or a drug) and responses. Moreover, understanding the relationship between the subjective sensitivity to drugs and responses does not entirely depend on the potential receptor mechanisms underlying this stimulus control [13][14][15].

The scholarly inquiry into the stimulus attributes of pharmacological compounds inaugurated with investigations into state-dependent learning during the initial semesters of the twentieth century, progressively metamorphosing into an innovative drug discrimination methodology. Organisms, encompassing homo sapiens, are capable of discerning the existence of pharmacological agents, and upon acquisition of this knowledge, these agents can function as discriminative stimuli, signifying the presence or absence of drug reinforcement (that is to say, whether the reinforcing consequences of the drug utilized during the training phase bear resemblance)[16][17][18][19]. Differences in these behavioral signals are utilized to study the discriminative effects of drugs. For instance, training rats to discriminate methamphetamine (MA) from saline, upon successful training, administration of MA or drugs producing similar discriminative stimulus to MA, rats will choose the corresponding lever (nose poke); whereas administration of saline or drugs not producing similar MA discriminative stimulus will lead to choosing the other lever (nose poke).

2.2. Drug Discrimination Procedures

Drug discrimination procedures generally refer to the procedures required to train animals to discriminate drug stimuli. Early drug discrimination research involved T-maze drug discrimination procedures, which evolved into double-lever operant drug discrimination procedures in the 1970s, greatly enhancing sensitivity to drugs, with doses required for stimulus effects much lower than those in T-maze and other behavioral tests [20][21][22].

Currently, drug discrimination procedures have been utilized across various species, with the most common including pigeons, rats, and mice, also extending to non-human primates and humans themselves. The training apparatus for drug discrimination generally employs Skinner operant boxes, with lever pressing or nose poking as the primary mode of operant behavior, utilizing fixed-ratio schedules for training. Drug discrimination procedures typically consist of three stages: initial training, discrimination training, and testing. Establishing drug discrimination requires prolonged training for organisms to accurately learn to recognize the effects and doses of a drug (or a combination of drugs), referred to as the training drug. Response rates in drug discrimination training can reveal the stimulant or inhibitory effects induced by drugs, while lever or nose poke choices by animals indicate differences in drug-induced stimuli, which are determined to be subjective rather than objective attributes.

The process of drug discrimination training is also a process of learning and memory. Theoretically, almost all psychoactive drugs acting on the central nervous system may possess discriminative stimulus properties. For example, all drugs abused by humans, antipsychotics, anxiolytics, antidepressants, etc., can be used as training drugs for drug discrimination research. The speed of drug discrimination formation varies significantly depending on the drug, dose, and species of animals; typically, acquiring drug discrimination stimuli requires several to dozens of training cycles, and once formed, they can remain stable for several years or even decades, limited by the lifespan of the animals.

3. Characteristics and Applications of Drug Discrimination Technique

3.1 Subjective Effects of Drug Discrimination

It is broadly posited that the discriminative stimulus attributes of pharmacological substances could be wholly or partially predicated upon their subjective impacts. In the case of non-human organisms, the discriminative stimulus characteristics of substances are profoundly correlated with their subjective influences on human entities. This facet is deemed the most invaluable element of the drug discrimination approach, as it represents the sole methodology presently available that facilitates the comprehension of how non-human beings perceive (or sense) the subjective ramifications following the administration of drugs. [23][24][25].

Almost all abused drugs produce discriminative stimuli in animals, exhibiting high pharmacological selectivity and specificity. Typically, only drugs with pharmacological mechanisms similar to the training drug can fully substitute for the training drug. For example, fentanyl, carfentanil, and heroin are selective μ-opioid receptor agonists. Fentanyl (19 $\mu g \cdot kg^{-1}$) can establish a stable drug discrimination model in rats. Fentanyl (1.0 35.0 μg·kg-1), carfentanil (0.1 3.9 $\mu g \cdot kg^{-1}$), and heroin (10.0 399.0 $\mu g \cdot kg^{-1}$) exhibit dose-dependent effects. The results suggest that fentanyl, carfentanil, and heroin may

have similar abuse potential, with the subjective effects speculated to be carfentanil > fentanyl > heroin. Thus, in addition to determining whether test drugs produce similar discriminative stimuli to training drugs, the potency of subjective effects can be inferred through the median effective dose (ED50) on drug dose-response curves.

3.2. Temporal Effects of Drug Discrimination

Drug discrimination technique provides a convenient and effective method to study the temporal effects of acute drug actions. Early studies trained male rats to distinguish between 5 $mg \cdot kg^{-1}$ morphine and saline in an avoidance shock paradigm, revealing that morphine injection produced discriminative stimulus effects 45 minutes after injection, with a time-dependent effect; the stimulus effect disappeared 3.6 hours after injection, similar to saline. Recent studies established a rat model for discriminating the primary psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC), analyzing the timing of different routes of administration (ROA) such as intraperitoneal injection, oral administration, subcutaneous injection, and inhalation. The results showed that THC inhalation had the fastest onset and the shortest duration of discriminative stimulus effects, while intraperitoneal injection had a slower onset and the longest duration [26][27][28][29]. Cannabis users typically smoke or ingest cannabis orally, while in rodent studies, cannabinoids are usually administered via injection. This research on the corresponding effects of ROA on THC abuse provides a basis for selecting the route of administration for THC behavioral pharmacology research. Additionally, using animal models that simulate relevant ROA may help predict drug effects on humans more accurately.

3.3. Stereoselectivity in Drug Discrimination

Many drugs are composed of enantiomers (stereoisomers), where enantiomers are compounds with the same molecular formula but different structures. However, these enantiomers exhibit differences in pharmacological action or discriminative stimulus properties [9]. The main component of illegal "bath salts," 3,4-methylenedioxypyrovalerone (MDPV), is a synthetic cathinone substance. Previous studies trained Sprague-Dawley rats to discriminate MDPV (0.5 mg·kg-1) from saline, assessing MDPV and its enantiomers, as well as other synthetic cathinone substances [alpha-pyrrolidinovalerophenone (α-PVP), 4-methylmethcathinone (4-MMC)] for subjective substitution effects. The results showed that (S)-MDPV, α-PVP, and 4-MMC produced complete substitution effects similar to racemic MDPV, while (R)-MDPV failed to substitute even at doses up to 5 mg·kg-1. The discriminative stimulus properties of drugs exhibit stereoselectivity, which contributes to understanding the discriminative stimulus properties of drug enantiomers. One enantiomer may be stronger than another (i.e., stereoselective), or one enantiomer may exhibit similar properties to the parent drug, adequately reflected in drug discrimination stimuli.

Drug discrimination technique is highly suitable for studying structure-activity relationships and evaluating the pharmacological activity of drug chemical structures. Through drug discrimination technique research, our laboratory discovered that synthetic cathinone substances such as α-PVP, 4-chloro-α-pyrrolidinopentiophenone (4-Cl-α-PVP), and 4-chloro-α-pyrrolidinopropiophenone (4Cl-α-PPP) can produce discriminative stimulus effects similar to MA. It is speculated that these substances may have similar abuse potential as MA in humans, with subjective effects ranked as α-PVP ≈ MA

> 4-Cl-α-PVP > 4-Cl-α-PPP. The addition of chlorine structures on the phenyl ring may decrease the discriminative stimulus effects of these structurally related cathinones [30][31][32][33].

3.4. Receptor Mechanisms and Effects on Discriminative Stimuli

The discriminative stimulus properties of drugs also reflect the specific central nervous system distribution and effects of neurotransmitter receptors. Research on the discriminative stimulus properties of drugs and their transduction mechanisms provides important insights into brain-behavior relationships [34][35][36]. The use of drug discrimination technique allows the study of the psychopharmacological mechanisms of drugs by comparing the effects of different receptor antagonists on drug discriminative stimulus effects to determine the roles of receptors and receptor subtypes [37][38][39][40]. For example, studying the effects of selective gamma-aminobutyric acid type A (GABAA) receptor subtype agonists or antagonists on propofol discriminative stimulus effects revealed that intraperitoneal injection of the α1 subunit-selective GABAA receptor agonist CL218872 (1-3 mg·kg^{-1}) and the α2/3 GABAA receptor-selective agonist SL651498 (0.3-3 mg·kg^{-1}) partially substituted for the discriminative stimulus effects of propofol. Meanwhile, the α2/3/5 GABAA receptor-selective agonist L838417 (0.2-0.6 mg·kg^{-1}) produced nearly 100% propofol discriminative effects. Additionally, the α5 GABAA receptor antagonist L655708 dose-dependently attenuated propofol discriminative stimuli. These results suggest that propofol produces discriminative stimulus effects in a dose-dependent manner, primarily acting on α5 subunit GABAA receptors.

Microinjection methods can be used to determine the potential central sites and receptor mechanisms mediating drug discriminative stimulus properties. Low doses of morphine injected into the ventral tegmental area (VTA) of the midbrain produce morphine discriminative effects, with only partial effects when injected into the periaqueductal gray and no effects in the striatum. Pre-administration of κ receptor agonist U69593 can block morphine discriminative effects, with no substitutive effects itself. It has a blocking effect in the periaqueductal gray but not in the VTA and striatum, suggesting that morphine's subjective effects are blocked by κ receptor agonists in the periaqueductal gray, and endogenous potassium ions and the opioid peptide system may have physiological antagonistic effects. However, these mechanisms may vary due to species differences, and caution should be exercised in extrapolating findings from animal studies to humans.

3.5. Individual Differences in Drug Discrimination

In drug discrimination research, there are individual differences in the sensitivity of subjects to drug discriminative stimulus properties, which often reflect the number of training cycles required for individual subjects to achieve discrimination criteria, i.e., some subjects will learn drug discrimination more quickly than others. Early recognition of the influence of discrimination speed on the sensitivity of training drug discrimination clues to ED50 has been noted. Herr et al. found interesting differences between male and female rats in LSD discriminative experiments, with dopamine antagonists exerting stronger rate-inhibiting effects in male rats and requiring lower doses of the serotonin antagonist MDL100907 to completely block stimulus effects. Nicotine animal discrimination studies have shown that individual differences may be

related to genetic differences, as the absence of the α7 nicotinic acetylcholine receptor gene may affect nicotine discriminative stimulus properties. Additionally, higher training doses result in a reduced number of training cycles required, with a higher ED50 value on dose-response curves. Therefore, the number of cycles required to reach training standards should be routinely provided information in research.

3.6. Drug Classification and Development

Drug discrimination technique has high pharmacological specificity and can be used to create drug classifications based on shared discriminative stimulus properties. Several categories have been determined based on extensive discriminative stimulus property research drugs, including: (1) central sedatives (barbiturates, etc.); (2) central anticholinergic drugs (especially antimuscarinic drugs); (3) nicotine; (4) cannabis (Δ9-tetrahydrocannabinol); and (5) hallucinogens (such as mescaline and LSD).

Drug discrimination technique is also frequently used in the behavioral pharmacology of new compounds and collaborates with national drug control agencies to determine and evaluate the abuse potential of drugs. For example, the Addiction Research Laboratory in the United States uses this method to conduct related research on the addictive and abusive potential of various synthetic cathinone substances. This laboratory, in collaboration with the National Narcotics Laboratory of the Ministry of Public Security, also uses this technique to evaluate the psychotropic dependence of cathinone substances. However, there are certain limitations to the drug discrimination technique in evaluating the abuse potential of drugs, such as long training times, lack of face validity, partial pharmacological effects that produce discriminative stimuli may not necessarily overlap with the neuropharmacological effects that cause drug abuse (masking phenomenon), etc. Compared with self-administration techniques, drug discrimination techniques have their advantages and disadvantages. When evaluating the psychotropic dependence of abused drugs, drug discrimination techniques combined with other behavioral pharmacology techniques, such as self-administration, provide a more comprehensive assessment.

Study of drug action mechanisms requires an understanding of reactions induced by drugs both in vivo and in vitro. Given the utility and value of preclinical behavioral analysis in the drug development process, behavioral and temporal analysis of drug discrimination is equally important. Both methods should proceed in parallel in discovering and developing new therapeutic drugs.

4. Outlook

The drug discrimination technique utilizes the physiological changes induced by psychoactive drugs in the nervous system, eliciting implicit perceptual stimulus effects. Through reinforcing specific behaviors (such as lever pressing) in the presence or absence of such stimuli, training is conducted to determine the presence and timing of subjective effects. Drug discrimination models offer the advantages of pharmacological specificity and predictive validity, providing a stable and unique method for studying the in vivo effects of drugs, especially in the application of investigating novel

psychoactive substances such as hallucinogens and cannabis-related drugs, which have advantages over other behavioral pharmacology techniques.

The rat discrimination models for hallucinogens LSD and mescaline were successfully established as early as 1971. Although many mechanisms regarding the implicit perceptual stimulus effects of these hallucinogens remain unclear, the 5-HT2A receptor subtype has been confirmed as necessary, with recent evidence suggesting the involvement of the 5-HT5A receptor subtype in the perceptual stimulus effects of these substances. With advancements in technology in the fields of structural chemistry, molecular biology, and genetic engineering, the medicinal value of hallucinogens has been rediscovered, and in conjunction with drug discrimination techniques, ongoing exploration of the pharmacological actions of hallucinogens and related psychedelics is possible. For instance, in hallucinogen discrimination models, specific gene expression can be explored for its mechanistic role in the perceptual stimulus effects of selected drugs, as well as studying individual differences in treatment outcomes and potential differences in sensitivity to side effects. Additionally, assessing gender differences in the implicit perceptual stimulus effects of hallucinogens represents a potential valuable avenue for future research. Furthermore, combining evaluations of genetic and gender differences with structural activity and mechanistic studies of hallucinogens further provides information for potential clinical research on hallucinogens.

The endocannabinoid (eCB) system, considered to be the most widely distributed system in the human body, has been shown to play roles in various physiological and pathological processes such as neural development, immunity, pain, cognition, sleep, stress responses, learning, memory, and drug abuse. Research and development of relevant therapeutic drugs target the eCB system. The eCB system consists of cannabinoid receptor type 1 (CB1R), cannabinoid receptor type 2 (CB2R), eCBs, and their synthesis/degradation enzymes. Compared to other abused drugs, establishing stable self-administration behaviors for psychoactive cannabinoids is challenging. To date, successful self-administration behaviors for THC have only been established in squirrel monkeys, with no reports on self-administration behaviors in rodent species. However, THC discrimination models are easily established in different animal species. Psychoactive cannabinoids bind to and activate CB1R, forming the basis for their discriminative stimulus effects. Therefore, drug discrimination technique becomes the most effective and pharmacologically selective animal model for studying abuse-related properties of cannabinoids. Since the 1970s, THC discrimination models have been used to research the discovery of cannabinoids and related antagonists, and the recent surge of literature related to cannabinoid discrimination further demonstrates its value as a scientific method for evaluating cannabinoid psychotropic dependence.

5. Conclusion

Drug discrimination techniques offer valuable insights into the pharmacological effects of psychoactive substances, particularly hallucinogens and cannabinoids. These techniques, leveraging implicit perceptual stimulus effects, provide a stable and specific method for studying the in vivo effects of drugs. While the mechanisms underlying the perceptual stimulus effects of hallucinogens like LSD and mescaline are still being elucidated, advancements in technology allow for continued exploration of their pharmacological actions. Similarly, research into the endocannabinoid system and psychoactive cannabinoids benefits from drug discrimination models, offering a pharmacologically selective approach to

studying abuse-related properties. By combining genetic, gender, and structural activity studies with drug discrimination techniques, a comprehensive understanding of the behavioral and physiological effects of psychoactive substances can be achieved, informing potential clinical research and therapeutic interventions. Thus, drug discrimination techniques remain indispensable tools in the study of psychoactive drugs and their effects on the nervous system.

Statements and Declarations

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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