Drug-Addiction and Drug-Dependency 10

Charles P. France

Contents

10.1 Drug Addiction and Drug Dependency

10.1.1 General Considerations

Drug abuse is a complex phenomenon, and many factors (e.g., availability, cost) contribute to whether a particular drug will be abused by a particular individual. Nevertheless, many drugs that are abused have common neurobiological and behavioral effects. Consequently, some of the properties of drugs that contribute to abuse can be examined systematically in animals using well-established and validated behavioral procedures. A major strength of this area of research is that the effects of drugs in these procedures (i.e., in nonhuman species) are highly predictive of the effects of the same drugs in humans; thus, behavioral assessments are used both to study the underlying biological and behavioral phenomena associated with drug abuse (e.g., drug reinforcement, physical dependence) and to assess whether new chemical entities have properties in animals that would indicate a likelihood of abuse in humans. Preclinical abuse and dependence liability studies typically comprise the following approaches and procedures:

- Physical dependence
- Tolerance
- Drug discrimination
- Self-administration
- Conditioned place preference

No single procedure or any set of procedures can exactly predict whether a drug is likely to be abused. However, when considered within the context of other known properties of the drug (e.g., receptor binding, pharmacokinetic profile), results of behavioral studies

C.P. France
Department of Pharmacology, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

H.G. Vogel et al. (eds.), *Drug Discovery and Evaluation: Safety and Pharmacokinetic Assays*,
DOI 10.1007/978-3-642-25240-2_10,

can be very useful in estimating the likelihood that new chemical entities will be abused, largely by comparing (in standardized assays) those new entities to reference compounds and known drugs of abuse.

10.1.2 Physical Dependence Studies

PURPOSE AND RATIONALE

Withdrawal phenomena, either after abrupt cessation of chronic treatment or after administration of a pharmacologic antagonist (e.g., naltrexone), can be observed in a variety of nonhuman species. Importantly, the withdrawal that emerges in some nonhumans topographically resembles important features of withdrawal in humans. On this basis, tests for drug dependence and withdrawal have been developed for monkeys (Seevers 1936; Seevers and Deneau 1963; Aceto 1990; Woods et al. 1993), dogs (Martin et al. 1974, 1976), rats (Buckett 1964; Cowan et al. 1988), and mice (Way et al. 1969; VonVoigtlander and Lewis 1983). Two general approaches are used to evaluate physical dependence potential: primary physical dependence and single-dose substitution. In the former, a test substance is administered repeatedly over days, and the assessment of dependence (i.e., by the emergence of withdrawal) occurs either after discontinuation of drug treatment or by administration of a pharmacologic antagonist. Precipitated withdrawal studies are warranted only when the mechanism or site of action of the test substance is known and when an appropriate pharmacologic antagonist is available. In a single-dose substitution study, a reference substance (e.g., morphine) is administered repeatedly over a sufficient number of days to produce dependence; after discontinuation of treatment with the reference substance, and when reliable withdrawal signs have emerged, the test substance is assessed for its ability to attenuate withdrawal signs. In this type of study, the test substance can be administered just once to assess its acute withdrawal-reversing effects or can be administered repeated over days (i.e., replace the reference substance) and subsequently discontinued followed by assessment of withdrawal signs.

A well-established in vitro procedure has also been used to test for opioid dependence (i.e., antagonist-precipitated withdrawal) in opioid-treated guinea pig ileum (Villarreal et al. 1977; Rodríguez et al. 1978; Collier et al. 1981; Cruz et al. 1991).

PROCEDURES

10.1.2.1 Opioid Withdrawal Responses in the Guinea Pig Ileum Made Dependent In Vitro

A 40-cm-long segment of the small intestine of male guinea pigs weighing 600–900 g is removed and placed in a low-magnesium Krebs solution. The terminal section of the guinea pig ileum is used after discarding the portion of 10 cm closest to the ileocecal junction. The ileum is cut in eight 3-cm-long segments. The intestinal content is gently removed with the aid of a glass rod. To produce opioid dependence, segments are incubated in 500-ml Erlenmeyer flasks containing 480 nM morphine in 250 ml Krebs solution saturated with a 95% O_2/5% CO_2 gas mixture at a temperature ranging between 4°C and 6°C for 1–48 h. One hour before completion of the incubation time, the segments are removed, placed in glass chambers with 50 ml Krebs solution bubbled with 95% O_2/5% CO_2 gas mixture at 36°C, and mounted on a vertical electrode with one edge fixed to the chamber plug and the opposite fixed to an isometrical force transducer (Grass FT 03) connected to a polygraph for recording the contractile activity of the longitudinal muscle. The ilea are set up with an initial tension of 1 g and left for a period of 30 min for stabilization. Thereafter, all segments are electrically stimulated with supramaximal rectangular pulses (10–40 V) of 0.5-ms duration at a frequency of 0.1 H.

Five minutes before naloxone administration, the electrical stimulation is suspended. The response to naloxone is recorded by administration of up to 100 nM. The response to the antagonist is recorded for 20 min, and thereafter the electrical stimulation is reinitiated and maintained for 10 min.

Thirty-five minutes after naloxone administration, various doses of nicotine are administered to provide a positive control. For comparison, a concentration-response curve for nicotine (1, 1.78, 3.2, 5.6, 10, 17.8, 32, and 56 μM) is obtained in untreated ilea. Moreover, the concentration-response curve for nicotine is obtained in ilea that are treated as follows: (1) exposed to 10 nM naloxone for 20 min, (2) exposed to 480 nM of morphine for 1 h, or (3) pretreated for 10 min with 3 or 10 nM of naloxone and exposed to 480 nM of morphine for 1 h. The response to nicotine is attenuated after pretreatment with morphine, and this attenuation is dose dependently antagonized by naloxone.

A correlation between the response to supramaximal electrical stimulation and the withdrawal response (contraction) precipitated with 100 nM naloxone as well as a correlation between withdrawal and nicotine response after long-term exposure (12–48 h) with 480 nM morphine is used to determine whether physical dependence developed and, therefore, whether the naloxone-induced contraction indicates withdrawal.

10.1.2.2 Test for Physical Dependence in Rats

Male albino rats receive either morphine or saline i.p. twice daily. The starting dose of morphine is 20 mg/kg and is increased by 40 mg/kg increments daily until, by day 11, the dose is 400 mg/kg. Maintenance at 400 mg/kg is continued through day 20. The test compound is similarly administered to groups of ten rats each, typically in ascending doses and a maximally tolerated dose. The daily increments have to be adjusted to a maximum level that is not lethal for the duration of the experiment.

Primary physical dependence capacity is measured on days 11 and 17 when all animals receive an injection of 10 mg/kg of naltrexone or naloxone i.p. in the morning. Signs of withdrawal are recorded during a 30- to 60-min period. Rats are scored for the presence or absence of withdrawal signs (e.g., diarrhea, wet-dog-type shaking) using standardized scoring.

A single-dose substitution study substitutes either a single dose or multiple doses (from day 20 through day 23) of the test substance in morphine-dependent rats; scoring for suppression of withdrawal occurs on days 20–23 and after discontinuation of the test substance.

10.1.2.3 Test for Physical Dependence in Monkeys

Groups of 3–4 rhesus monkeys (3–6 kg body weight) receive morphine four times daily (s.c. or i.m.) beginning with a dose of 1.0 mg/kg. Progressively, the unit dose is increased to a final dose of 3.2 mg/kg/6 h. The test substance is similarly administered to groups of 3–4 monkeys. For the test compound, the daily increments in drug administration are adjusted to a maximally tolerated (nontoxic) dose and frequency of injection. Both groups of monkeys are then maintained at their appropriate dose levels for a minimum of 112 days. On days 35, 60, and 91, 1 mg/kg of naltrexone or naloxone is administered (s.c. or i.m.) in the morning. On days 50 and 112, all doses are omitted for 24 h. Signs of withdrawal are recorded during a 30- to 60-min period using standardized scoring (e.g., Katz 1986; Becker et al. 2008; Brandt and France 1998).

CRITICAL ASSESSMENT OF THE METHOD

The emergence of withdrawal signs after discontinuation of drug treatment is dependent of the duration of action of the treatment compound. Thus, after discontinuation of morphine treatment, withdrawal reliably emerges within 12–24 h. For drugs with an unusually long duration of action (e.g., buprenorphine), observations for withdrawal signs need to occur over longer periods of time (e.g., several days); for drugs with an exceptionally long duration of action, the gradual and prolonged offset of drug action might preclude emergence of significant withdrawal, despite development of dependence. Opioid antagonists will precipitate withdrawal in animals treated with opioid agonists. If a test substance has actions at non-opioid receptors, a negative result with naltrexone or naloxone in a precipitated withdrawal study might not provide useful information regarding dependence potential. Thus, both precipitated withdrawal and treatment discontinuation-induced withdrawal need to be studied for test compounds.

Rhesus monkeys have been used extensively for assessing physical dependence potential of opioid receptor agonists. An excellent correlation between humans and rhesus monkeys has been shown regarding the physical dependence liability of opioids, although there are some compounds for which the relative potency between humans and monkeys is not what is predicted from other data.

Nonhuman species can also be used to assess physical dependence potential of other classes of drugs, including sedative/hypnotics such as benzodiazepines and barbiturates. Physical dependence potential alone cannot be assumed to predict abuse liability because some drugs that are not abused (e.g., kappa opioid receptor agonists) can produce marked physical dependence (Gmerek et al. 1987) and discontinuation of some widely used therapeutic drugs (selective serotonin reuptake inhibitors) can result in a discontinuation syndrome that does not appear to promote drug taking (Black et al. 2000; Hosenbocus and Chahal 2011).

MODIFICATIONS OF THE METHODS

Mouse jumping as a simple screening method to estimate the physical dependence capacity of opioid agonists has been recommended by Saelens et al. (1971). Mice receive seven i.p. injections over 2 days. The test compound is given at doses increasing in multiples of two until a maximally tolerated dose is reached. Two hours after the last injection, the animals receive an i.p. injection of 100 mg/kg naloxone and are placed individually into glass cylinders. The number of jumps is recorded during 10 min.

Rothwell et al. (2011) used acoustic startle reflex and conditioned place aversion to examine long-lasting changes in behavior caused by a single injection of naloxone at different times after a single injection of morphine.

Opioid-receptor agonist-induced dependence can be studied by measuring withdrawal in the guinea pig ileum made dependent in vitro (Cruz et al. 1991).

Kest et al. (2002) compared naloxone-precipitated withdrawal jumping in several strains of mice after acute or multiple injections of morphine or after chronic infusion of morphine with osmotic minipumps.

Becker et al. (2010) used Pavlovian conditioning to demonstrate the ability of environmental stimuli that are paired with the administration of naloxone to elicit withdrawal in morphine-dependent rats.

Yoshimura et al. (1993) studied physical dependence on morphine induced in dogs via the use of osmotic minipumps. Naloxone-precipitated withdrawal signs were recorded such as hyperactivity, biting, digging, tremors, nausea, hyperthermia, increased wakefulness, and by EEG activation in the amygdala and hippocampus, followed by a dissociation of the EEG in the cortex (fast wave) from that in the limbic (slow wave) system, increased heart rate and raised blood pressure. Withdrawal signs were more severe in animals with osmotic minipumps than in those receiving the same dose by syringe injections.

Pierce and Raper (1995) studied the effects of laboratory handling procedures on naloxone-precipitated withdrawal behavior in morphine-dependent rats, and Gellert and Holtzman (1978) used access to drug in drinking solutions to study morphine dependence and withdrawal in rats.

Pierce et al. (1996) used slow release emulsion formulations of methadone to induce dependence in rats. Withdrawal was induced following i.p. challenge with either naloxone or saline, and dependence was assessed in terms of the presence or absence of characteristic withdrawal signs.

Antagonist-precipitated and discontinuation-induced withdrawal in morphine-dependent rhesus monkeys was studied by Becker et al. (2008) using several behavioral procedures as well as telemetry. Changes in heart rate and body temperature persisted for much longer (several weeks) than other directly observable indices of withdrawal or discriminative stimulus effects.

Korkmaz and Wahlström (1999) used EEG threshold and sensitivity to hexobarbital to compare withdrawal in rats treated for different durations with benzodiazepines such as diazepam and lorazepam.

Gallaher et al. (1986) used directly observable changes in behavior to characterize withdrawal in mice that consumed diazepam for 53 days (as much as 1,000 mg/kg/day) in laboratory chow.

McMahon et al. (2007) compared directly observable behavioral effects, rate of operant responding, discriminative stimulus effects, and serum drug concentration to characterize withdrawal after discontinuation of chronic treatment with diazepam in rhesus monkeys.

Stewart and McMahon (2010) compared directly observable behavioral effects and discriminative stimulus effects to withdrawal-like behavior produced by administration of the cannabinoid receptor antagonist rimonabant in rhesus monkeys treated chronically with the cannabinoid receptor agonist delta-9-tetrahydrocannabinol.

Weerts et al. (2005) demonstrated dependence to gamma hydroxybutyrate, and Goodwin et al. (2006) demonstrated dependence to gamma-butyrolactone in baboons using directly observable behavioral effects after administration of an antagonist and after discontinuation of chronic drug treatment.

References and Further Reading

Aceto MD (1990) Assessment of physical dependence techniques for the evaluation of abused drugs. In: Adler MW, Cowan A (eds) Testing and evaluation of drugs of abuse, vol 6, Modern methods in pharmacology. Wiley-Liss, New York, pp 67–79

Becker GL, Gerak LR, Koek FCP (2008) Antagonist-precipitated and discontinuation-induced withdrawal in morphine-dependent rhesus monkeys. Psychopharmacology 201:373–382

Becker GL, Gerak LR, Li JX, Koek W, France CP (2010) Precipitated and conditioned withdrawal in morphine-treated rats. Psychopharmacology 209:85–94

Black K, Shea C, Dursun S, Kutcher S (2000) Selective serotonin reuptake inhibitor discontinuation syndrome: proposed diagnostic criteria. J Psychiatry Neurosci 25:255–261

Brandt MR, France CP (1998) Chronic l-alpha acetylmethadol in rhesus monkeys: discriminative stimulus and other behavioral measures of dependence and withdrawal. J Pharmacol Exp Ther 287:1029–1037

Buckett WR (1964) A new test for morphine-like physical dependence (addiction liability) in rats. Psychopharmacologia 6:410–416

Deneau GA, Seevers MH (1964) Drug dependence. In: Laurence DR, Bacharach AL (eds) Evaluation of drug activities: pharmacometrics. Academic, London/New York, pp 167–179

Collier HOJ, Cuthbert NJ, Francis DL (1981) Effects of time and drug concentration on the induction of responsiveness to naloxone in guinea pig ileum exposed to normorphine in vitro. Br J Pharmacol 332P–333P

Cowan A, Zhu XZ, Mosberg HI, Omnaas JR, Porreca F (1988) Direct dependence studies in rats with agents selective for different types of opioid receptor. J Pharmacol Exp Ther 246:950–955

Cruz SL, Salazar LA, Villarreal JE (1991) A methodological basis for improving the reliability of measurements of opiate abstinence responses in the guinea pig ileum made dependent in vitro. J Pharmacol Methods 25:329–342

Gallaher EJ, Henauer SA, Jacques CJ, Hollister LE (1986) Benzodiazepine dependence in mice after ingestion of drug-containing food pellets. J Pharmacol Exp Ther 237:462–467

Gellert VF, Holtzman SG (1978) Development and maintenance of morphine tolerance and dependence in the rat by scheduled access to morphing drinking solutions. J Pharmacol Exp Ther 205:536–546

Gmerek DE, Dykstra LA, Woods JH (1987) Kappa opioids in rhesus monkeys. III. Dependence associated with chronic administration. J Pharmacol Exp Ther 242:428–436

Goodwin AK, Griffiths RR, Brown PR, Froestl W, Jakobs C, Gibson KM, Weerts EM (2006) Chronic intragastric administration of gamma-butyrolactone produces physical dependence in baboons. Psychopharmacology 189:71–82

Hosenbocus S, Chahal R (2011) SSRIs and SNRIs: a review of the discontinuation syndrome in children and adolescents. J Can Acad Child Adolesc Psychiatry 20:60–67

Katz JL (1986) Effects of clonidine and morphine on opioid withdrawal in rhesus monkeys. Psychopharmacology 88:392–397

Kest B, Palmese CA, Hopkins E, Adler M, Juni A, Mogil JS (2002) Naloxone-precipitated withdrawal jumping in 11 inbred mouse strains: evidence for common genetic mechanisms in acute and chronic morphine physical dependence. Neuroscience 115:463–469

Korkmaz S, Wahlström G (1999) Physical dependence after benzodiazepine treatments in rats: comparison of short and long treatments with diazepam and lorazepam. J Stud Alcohol 60:546–554

Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE (1976) The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther 197:517–532

Martin WR, Eades CG, Thompson WO, Thompson JA, Flanary HG (1974) Morphine physical dependence in the dog. J Pharmacol Exp Ther 189:759–771

McMahon LR, Javors MA, France CP (2007) Changes in relative potency among positive GABA(A) receptor modulators upon discontinuation of chronic benzodiazepine treatment in rhesus monkeys. Psychopharmacology 192:135–145

Pierce TL, Raper C (1995) The effects of laboratory handling procedures on naloxone-precipitated withdrawal behavior in morphine-dependent rats. J Pharmacol Toxicol Methods 34:149–155

Pierce TL, Hope W, Raper C (1996) The induction and quantitation of methadone dependence in the rat. J Pharmacol Toxicol Methods 36:137–146

Rodríguez R, Luján M, Campos AE, Chorné R (1978) Morphine-dependence in the isolated guinea pig ileum and its modification by p-chlorophenylalanine. Life Sci 23:913–920

Rothwell PI, Thomas MJ, Gewirtz JC (2011) Protracted manifestations of acute dependence after a single morphine exposure. Psychopharmacology (Epub ahead of print) PMID:21833504

Saelens JK, Granat FR, Sawyer WK (1971) The mouse jumping test: a simple screening method to estimate the physical dependence capacity of analgesics. Arch Int Pharmacodyn Ther 190:213–218

Seevers MH (1936) Opiate addiction in the monkey. I. Methods of study. J Pharmacol Exp Ther 56:147–156

Seevers MH, Deneau GA (1963) In: Root WS, Hoffman FG (eds) Physiological Pharmacology, vol I. Academic, New York/London, p 565

Stewart JL, McMahon LR (2010) Rimonabant-induced delta9-tetrahydrocannabinol withdrawal in rhesus monkeys: discriminative stimulus effects and other withdrawal signs. J Pharmacol Exp Ther 334:347–356

Villarreal JE, Martinez JN, Castro A (1977) Validation of a new procedure to study narcotic dependence in the isolated guinea pig ileum. Bull Problems Drug Dependence, pp 305–314

VonVoigtlander PF, Lewis RA (1983) A withdrawal hyperalgesia test for physical dependence: evaluation of μ and mixed-partial opioid agonists. J Pharmacol Methods 10:277–282

Way EL (1993) Opioid tolerance and physical dependence and their relationship. In: Herz A, Akil H, Simon EJ (eds) Opioids II, vol 104, Handbook of experimental pharmacology. Springer, Berlin/Heidelberg/New York, pp 573–596, chapter 53

Way EL, Loh HH, Shen FH (1969) Simultaneous quantitative assessment of morphine tolerance and physical dependence. J Pharmacol Exp Ther 167:1–8

Weerts EM, Goodwin AK, Griffiths RR, Brown PR, Froestl W, Jakobs C, Gibson KM (2005) Spontaneous and precipitated withdrawal after chronic intragastric administration of gamma-hydroxybutyrate (GHB) in baboons. Psychopharmacology 179:678-687

Woods JH, France CP, Winger G, Bertamio AJ, Schwarz-Stevens K (1993) Opioid abuse liability assessment in rhesus

monkeys. In: Herz A, Akil H, Simon EJ (eds) Opioids II, vol 104, Handbook of experimental pharmacology. Springer, Berlin/Heidelberg/New York, pp 609–632, chapter 55
Yoshimura K, Horiuchi M, Konishi M, Yamamoto KI (1993) Physical dependence on morphine induced in dogs via the use of miniosmotic pumps. J Pharmacol Toxicol Methods 30:85–95

10.1.3 Tolerance Studies

PURPOSE AND RATIONALE

Repeated treatment with some drugs can decrease sensitivity to the effects of the same drugs (tolerance) and to the effects of pharmacologically related drugs (cross-tolerance). The development of tolerance can limit the effectiveness of drugs (e.g., analgesics), thereby necessitating an increase in the dose for recovery of the desired effect. The radiant heat or the hot plate method for testing antinociceptive activity of opioid receptor agonists in mice is adapted to measure drug-induced changes in the sensitivity to a noxious stimulus.

PROCEDURE

Male mice (10–12 per condition) with an initial weight of 18–20 g are used. They are placed in restraining cages. A noxious stimulus is produced by an intense light beam directed to the proximal part of the tail. The subject can respond to this stimulus by flicking its tail. The reaction time, the interval between stimulus onset and response, is measured automatically with commercially available equipment or manually with a stopwatch. A maximum time of exposure to the stimulus (e.g., 12-s cutoff time) prevents tissue damage. Prior to drug administration, two control measures of reaction time are obtained for each animal. After administration of the drug, the test is repeated 15, 30, and 60 min after s.c. injection or 30, 60, and 120 min after oral administration. In this way, time of peak activity can be determined. Mice showing a reaction time of the average control value plus two times the standard deviation in the control experiment are regarded as positive. Complete dose–response curves are determined, and ED_{50} values are calculated. Subsequently, the animals are treated for 5 days once every day with a dose which is four times higher than the ED_{50} in the first experiment. On the following day, dose–response curves are determined using at least three doses and the ED_{50} is calculated again. Frequency and duration of drug administration should be adjusted to insure adequate exposure for assessing tolerance. Cross-tolerance can be assessed in the same animals shown to be tolerant to one drug by determining a dose–response curve for a second drug.

EVALUATION

Reduced effectiveness of a fixed dose and/or the need for larger doses to obtain a constant response indicates the development of tolerance. ED_{50} values obtained before and after repeated daily treatment are compared to assess the magnitude of tolerance. Similarly, comparison of ED_{50} values for one drug, obtained in untreated animals and in animals treated with (and shown to be tolerant to) a second drug, is used to determine cross-tolerance.

CRITICAL ASSESSMENT OF THE TEST

Tolerance is observed with a variety of drugs including opioid receptor agonists, barbiturates, benzodiazepines, and ethanol. The measurement of antinociception after single and repeated administration, therefore, has to be regarded as a primary test. Moreover, a decrease in the potency of a drug after daily drug treatment, while providing evidence for tolerance, does not give insight to the mechanism by which tolerance has developed (i.e., pharmacodynamic, pharmacokinetic, behavioral). Demonstration that the antinociceptive effects of a new drug do not decrease after repeated daily treatment with high doses indicates that it is not necessary to escalate dose in order to maintain effectiveness and represents the first step for establishing the absence of tolerance liability. For drugs that do not have antinociceptive actions, other tests need to be employed using a similar dosing strategy for assessing tolerance and cross-tolerance.

MODIFICATIONS OF THE METHOD

Other authors (e.g., Glassman 1971) injected the dose which induced a full antinociceptive effect in mice twice daily for a period of 21 days and evaluated the stepwise decay of effectiveness. After 21 days, the effect of 10 mg/kg morphine or 30 mg/kg meperidine i.p. decreased to approximately 50% of the value of the first day.

Boisse et al. (1986, 1990) demonstrated tolerance and dependence to both short-acting (midazolam) and long-acting (chlordiazepoxide) benzodiazepines in rats.

Langerman et al. (1995) evaluated the acute tolerance to continuous morphine infusion up to 8 h in the

rat with various doses using the hot plate and the tail flick assay. Tolerance was observed with the hot plate assay but not with the tail flick assay suggesting tolerance development at a supraspinal site.

Smith et al. (2003) used twice-daily injections of morphine and implantation of morphine-containing pellets to study mechanisms of opioid tolerance in mice.

Riba et al. (2002) showed that the role of mu opioid receptors in modifying the antinociceptive effects of delta opioid receptor agonists changes during morphine tolerance.

Schwandt et al. (2008) report rapid tolerance to the motor impairing effects of ethanol in adolescent rhesus monkeys.

Eppilito and Gerak (2010) treated rats daily with the neuroactive steroid pregnenolone and showed tolerance to some, but not all, effects on operant responding for food.

References and Further Reading

Boisse NR, Periana RM, Guarino JJ, Druger HS, Samoriski GM (1986) Pharmacologic characterization of acute chlordiazepoxide dependence in the rat. J Pharmacol Exp Ther 239:775–783

Boisse NR, Quaglietta N, Samoriski GM, Guarino JJ (1990) Tolerance and physical dependence to a short-acting benzodiazepine, midazolam. J Pharmacol Exp Ther 252: 1125–1133

Eppilito AK, Gerak LR (2010) Tolerance to the rate-increasing and not rate-decreasing effects of pregnenolone in rats. Behav Pharmacol (Epub ahead of print) PMID:20859199

Glassman JM (1971) Agents with analgesic activity and dependence liability. In: Turner RA, Hebborn P (eds) Screening methods in pharmacology, vol II. Academic, New York/London, pp 227–248

Kalant H, Khanna JM (1990) Methods for the study of tolerance. In: Adler MW, Cowan A (eds) Testing and evaluation of drugs of abuse, vol 6, Modern methods in pharmacology. Wiley-Liss, New York, pp 43–66

Khanna JM, Mayer JM, Lê AD, Kalant H (1984) Differential response to ethanol, pentobarbital and morphine in mice specially bred for ethanol sensitivity. Alcohol 1:447–451

Langerman L, Zakowski MI, Piskoun B, Grant GJ (1995) Hot plate versus tail flick: evaluation of acute tolerance to continuous morphine infusion in the rat model. J Pharmacol Toxicol Methods 34:23–27

Riba P, Ben Y, Smith AP, Furst S, Lee NM (2002) Morphine tolerance in spinal cord is due to interaction between mu- and delta-receptors. J Pharmacol Exp Ther 300:265–272

Schwandt ML, Higley JD, Suomi SJ, Heilig M, Barr CS (2008) Rapid tolerance and locomotor sensitization in ethanol-naïve adolescent rhesus macaques. Alcohol Clin Exp Res 32:1217–1228

Smith FL, Javed RR, Elzey MJ, Dewey WL (2003) The expression of a high level of morphine antinociceptive tolerance in mice involves both PKC and PKA. Brain Res 985:78–88

10.1.4 Tests for Abuse Liability

10.1.4.1 General Considerations

Drug abuse often occurs in the absence of physical dependence. The term "psychological dependence" is often used to describe abuse-related phenomena that are not specifically related to physical dependence (Deneau 1964), and laboratory procedures have been developed in animals, not physically dependent on drugs, which are predictive of abuse-related effects in humans. For example, drug discrimination procedures are frequently used to complement other assays of abuse liability; discrimination procedures have the advantage of having a high degree of pharmacologic selectivity which can be used to identify mechanism of action (e.g., receptor type) or to compare mechanism of action between a reference substance and a test substance. Importantly, drug discrimination procedures are predictive of the subjective effects of drugs in humans (Holtzman 1983, 1990; Brady et al. 1987; Colpaert 1987; Overton 1987; Hoffmeister 1988). Self-administration procedures are used to study the reinforcing effects of drugs and are the procedures used most often for predicting abuse liability of new chemical entities (Deneau et al. 1969; Hoffmeister 1979; Littmann et al. 1979; Woolverton and Schuster 1983; Bozarth 1987; Meisch and Carroll 1987; Weeks and Collins 1987; Yokel 1987; Woolverton and Nader 1990). More recently, and in a more limited context, conditioned place preference procedures have been used to examine drug effects that might be predictive of abuse. Finally, based on the early observations of Olds and colleagues (Olds et al. 1956; Olds 1979) on intracranial self-stimulation, procedures have also been developed for studying drug-induced changes in brain-stimulation reward (Kornetsky and Bain 1990), although this methodology has not been used systematically with a sufficiently wide range of drugs for it to be included in a standard abuse liability assessment.

10.1.4.2 Drug Discrimination Studies

PURPOSE AND RATIONALE

Many laboratories use two-choice discrimination procedures to investigate the mechanism or site of action

of test substances by examining compounds in animals trained to discriminate a reference substance and known drug of abuse (Shannon and Holtzman 1976, 1986; Holtzman 1983, 1990; Brady et al. 1987; Colpaert 1987; Overton 1987; Hoffmeister 1988; Carboni et al. 1989). Because of the pharmacologic selectivity of this procedure, test substances might need to be assessed in different groups of animals trained to discriminate different reference substances (e.g., cocaine or heroin). Less common are studies in which animals are trained to discriminate a test substance (presumably with a mechanism[s] of action that is not fully known) and reference substances are examined for their ability to produce discriminative stimulus effects like the test substance.

PROCEDURE

Rats are trained to press one of two choice levers either to receive a food pellet or to avoid/escape electric foot shock which is delivered intermittently beginning 5 s after the start of the trial. The occurrence of a trial is signaled by the illumination of a light in the operant chamber. In some procedures, a third (observing) lever is mounted in the wall of the chamber opposite the two-choice levers and must be pressed before the choice response is made. This contingency prevents the rat from persevering on a single response lever; thus, the choice response in each trial is relatively independent of the consequences of choice responses in the preceding trials of the session. The rats are tested in 20-trial sessions. Animals are trained to discriminate a prototype of the drug of interest. Morphine and fentanyl have served well as training drugs for exploring the discriminative effects of prototypic mu opioid receptor agonists; however, many drugs from a variety of pharmacologic classes have been used as training stimuli in drug discrimination studies (see Glennon and Young 2011). Training often occurs more rapidly when the dose of the training drug is the largest dose that does not disrupt behavior. For discrimination training, the animal is placed in the operant chamber and trained to perform the required response, initially under a schedule of continuous reinforcement where a single response on either lever delivers a food pellet or postpones/terminates electric shock. As performance improves, the response requirement is increased progressively across days (e.g., to a maximum of 10 [fixed-ratio 10]), and discrimination training commences whereby responding on just one of the levers is reinforced in each session. In two-choice procedures, the left choice lever and the right choice lever are designated for drug and vehicle training sessions, respectively, for half of the animals in a group; the lever designation is reversed for the other half of the animals. Acquisition of the discrimination is a function of the drug, training dose, and the number of training sessions. Training continues until the subject reaches predetermined performance criteria, which typically could be the following: at least 80% of the total session responses on the injection (drug or vehicle) appropriate lever and less than one fixed-ratio value (e.g., 10) of responses on the injection-inappropriate lever prior to delivery of the first reinforcer (i.e., food pellet delivery or first postponement/termination of shock) for six consecutive training sessions. A morphine discrimination can be established in rats, according to these criteria, in 6–12 weeks. Once stable discrimination performance is achieved; tests of generalization to test substances can be interposed among the training sessions. During test sessions, the reinforcer is available after completion of the response requirement on either lever. Complete dose–response curves for the training drug and the test drug are obtained. In cases where the test drug does not produce responding on the training drug-appropriate lever, the test drug should be evaluated up to doses that decrease rates of lever pressing or until other behavioral effects are observed, in order to insure that the substance is evaluated up to behaviorally active doses. Drugs from a wide variety of classes have been used as training stimuli in these types of procedures and in a variety of species.

EVALUATION

Results of the stimulus-generalization test usually are evaluated with the quantitative or graded method, whereby the amount of responding on the training drug-associated lever is expressed as a percentage of the total number of responses during a test (i.e., responding on the drug-appropriate lever plus responding on the vehicle-appropriate lever). This percentage is compared with the percentage of drug-appropriate responses normally engendered by the training dose of the training drug (reference standard). The discriminative stimulus effects of the test drug substitute for those of the training drug if the maximal percentages of drug-appropriate responding are not significantly different from each other. When stimulus control of behavior transfers from one drug to another,

it can be inferred that the test drug produced discriminative stimulus effects that are similar to those of the training drug. Advantages of this procedure are that it is pharmacologically very selective and that the discriminative stimulus effects of drugs are related to and predictive of subjective effects in humans. When appropriate pharmacological tools (e.g., antagonists acting at the same receptor as the training drug) are available, the mechanism(s) mediating the discriminative stimulus effects of a drug can be confirmed by combining drugs (agonists with antagonists).

CRITICAL ASSESSMENT OF THE METHOD

Drug discrimination procedures display a high degree of pharmacologic selectivity. Test drugs that dose dependently occasion responding on the drug-appropriate lever likely share a mechanism of action with the training drug; drugs that do not occasion responding on the drug-appropriate lever likely are pharmacologically dissimilar to the training drug (in terms of site of action and/or in terms of efficacy) and will typically cause responding predominantly if not exclusively on the lever that is appropriate for the drug vehicle, up to behaviorally active doses. The pharmacologic selectivity of these procedures permits differentiation not only among compounds acting on different receptors or neurochemical systems (e.g., dopamine receptors vs. opioid receptors) but also among compounds acting on different subtypes of receptors within the same receptor class (e.g., mu vs. kappa opioid receptor agonists). Because of the importance of pharmacokinetic factors to the overall abuse liability of drugs, and because drug discrimination procedures are relatively insensitive to pharmacokinetic factors (as compared to self-administration procedures), positive results from a drug discrimination study are not in themselves sufficient to predict abuse liability. Along with other measures of drug action, results of drug discrimination studies are used to predict the likelihood of new compounds having abuse liability. Typically, self-administration data are used along with drug discrimination data, since these two assays are sensitive to different, though related aspects of drug activity. A negative effect with a test compound in a drug discrimination procedure indicates that the test substance, at the doses and pretreatment times studied, does not share discriminative stimulus effects with the training drug; it does not indicate that the test substance is devoid of discriminative stimulus effects or that the test substance is not likely to be abused. Thus, the high pharmacological selectivity of drug discrimination procedures is both an asset and a limitation.

MODIFICATIONS OF THE METHOD

Drug discrimination studies are performed in a variety of species including squirrel monkeys, rhesus monkeys, pigeons, gerbils, and mice (Hein et al. 1981; Herling and Woods 1981; Bertalmio and Woods 1987; Bertalmio et al. 1982; Dykstra et al. 1987, 1988; France and Woods 1993; France et al. 1994, 1995; Jarbe and Swedberg 1998; Shelton et al. 2004; Stolerman et al. 2004). Operant responding can be maintained with different reinforcers, including food, liquids, and aversive stimuli (e.g., electric shock). While the percentage of the total responses made on the drug-appropriate lever (averaged among subjects) is commonly used to express and analyze drug effects, some investigators express and analyze data in terms of the percentage of animals emitting some predetermined minimum (e.g., 90%) percentage of responses on the drug-appropriate lever.

The pharmacologic selectivity of drug discrimination procedures is particularly evident with opioid receptor agonists that bind selectively to different receptor subtypes. For example, monkeys trained to discriminate injections of a mu opioid receptor agonist (codeine, etorphine, or alfentanil) generalize to other mu opioid receptor agonists and not to non-opioid drugs, not to opioid receptor antagonists, and not to opioid receptor agonists acting at other (e.g., kappa) opioid receptors. Conversely, monkeys trained to discriminate a kappa opioid receptor agonist such as ethylketocyclazocine or U-50,488 generalize to other kappa receptor agonists and not to mu receptor agonists, antagonists, or to non-opioids (Woods et al. 1993; France et al. 1994).

Meert et al. (1989) used drug discrimination studies to characterize risperidone as an antagonist of the discriminative stimulus effects of LSD.

Meert and Janssen (1989) and Meert et al. (1990) showed differences between ritanserin and chlordiazepoxide in drug discrimination procedures.

Discrimination procedures have also been used to examine stimulus conditions that are believed to reflect drug withdrawal. Some of those procedures involve Pavlovian conditioning of aversive stimuli (Davis et al. 2009) whereas others involve operant procedures in which pharmacological antagonists are the training

stimuli in animals treated chronically with an agonist (Becker et al. 2008; Stewart and McMahon 2010).

Delta-9-tetrahydrocannabinol discrimination in rats was proposed as model for cannabis intoxication in humans (Balster and Prescott 1990).

The drug discrimination method has also been applied to study anxiolytic drugs using pentylenetetrazol at subconvulsive doses (Sherman and Lal 1979, 1980; Sherman et al. 1979; Lal and Sherman 1980).

The conditioned taste aversion procedure has been described as a more rapid alternative to two-lever operant procedures in drug discrimination research (Garcia et al. 1955; van Heest et al. 1992).

Others have studied combinations of drugs in animals trained to discriminate one or more drugs alone or in combination (McMillan et al. 2009; Stolerman et al. 1999).

References and Further Reading

Balster RL, Prescott WR (1990) Δ^9-Tetrahydrocannabinol discrimination in rats as a model for cannabis intoxication. Neurosci Behav Rev 16:55–62

Becker GL, Gerak LR, Koek W, France CP (2008) Antagonist-precipitated and discontinuation-induced withdrawal in morphine-dependent rhesus monkeys. Psychopharmacology 201:373–382

Bertalmio AJ, Woods JH (1987) Differentiation between μ and κ receptor mediated effects in opioid drug discrimination: apparent pA_2 analysis. J Pharmacol Exp Ther 243:591–598

Bertalmio AJ, Herling S, Hampton RY, Winger G, Woods JH (1982) A procedure for rapid evaluation of the discriminative stimulus effects of drugs. J Pharmacol Meth 7:289–299

Bozarth MA (1987) Intracranial self-administration procedures for the assessment of drug reinforcement. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 178–187

Brady JV, Griffiths RR, Hienz RD, Ator NA, Lukas SE, Lamb RJ (1987) Assessing drugs for abuse liability and dependence potential in laboratory primates. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 45–85

Carboni E, Acquas E; Leone P, di Chiara G (1989) 5-HT_3 receptor antagonists block morphine- and nicotine- but not amphetamine-induced award. Psychopharmacology 97:175–178

Colpaert FC (1987) Drug discrimination: methods of manipulation, measurement, and analysis. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 341–372

Colpaert FC, Janssen PAJ (1984) Agonist and antagonist effects of prototype opiate drugs in rats discrimination fentanyl from saline: Characteristics of partial generalization. J Pharmacol Exp Ther 220:193–199

Cruz SL, Salazar LA, Villarreal JE (1991) A methodological basis for improving the reliability of measurements of opiate abstinence responses in the guinea pig ileum made dependent in vitro. J Pharmacol Methods 25:329–342

Davis CM, Stevenson GW, Cañadas F, Ullrich R, Rice KC, Riley AL (2009) Discriminative stimulus properties of naloxone in Long-Evans rats: assessment with the conditioned taste aversion baseline of drug discrimination learning. Psychopharmacology 209:421–429

Deneau G, Yanagita T, Seevers MH (1969) Self-administration of psychoactive substances by the monkey. Psychopharmacologia 16:30–48

Deneau GA (1964) Pharmacological techniques for evaluating addiction liability of drugs. In: Nodine JH, Siegler PE (eds) Animal and clinical pharmacologic techniques in drug evaluation. Year Book Medical Publishers, Chicago, pp 406–410

Dykstra LA, Gmerek DE, Winger G, Woods JH (1987) Kappa opioids in rhesus monkeys. I. Diuresis, sedation, analgesia and discriminative stimulus effects. J Pharmacol Exp Ther 242:413–420

Dykstra LA, Bertalmio AJ, Woods JH (1988) Discriminative and analgesic effects of mu and kappa opioids: in vivo pA_2 analysis. In: Colpaert FC, Balster RL (eds) Transduction mechanisms of drug stimuli. Springer, Berlin/Heidelberg/New York, pp 107–121, Psychopharmacology series 4

France CP (1995) A sensitive, efficient drug discrimination procedure for studying *kappa* antagonists in rhesus monkeys. Analgesia 1:421–424

France CP, Woods JH (1993) U-50488, saline, naltrexone discrimination in U-50,488 treated pigeons. Behav Pharmacol 4:509–516

France CP, Gerak LR, Winger GD, Medzihradsky F, Bagley JR, Brockunier LL, Woods JH (1995) Behavioral effects and receptor binding affinities of fentanyl derivatives in rhesus monkeys. J Pharmacol Exp Ther 274:17–28

France CP, Medzihradsky F, Woods JH (1994) Comparison of *kappa* opioids in rhesus monkeys: behavioral effects and binding affinities. J Pharmacol Exp Ther 268:47–58

Garcia J, Kimmeldorf DJ, Koelling RA (1955) Conditioned taste aversion to saccharin resulting from exposure to gamma irradiation. Science 122:157–158

Glennon RA, Young R (eds) (2011) Drug discrimination: applications to medicinal chemistry and drug studies. Wiley, New Jersey

Hein DW, Young AM, Herling S, Woods JH (1981) Pharmacological analysis of the discriminative stimulus characteristics of ethylketazocine in the rhesus monkey. J Pharmacol Exp Ther 218:7–15

Herling S, Woods JH (1981) Discriminative stimulus effects of narcotics: evidence for multiple receptor-mediated actions. Life Sci 28:1571–1584

Hoffmeister F (1979) Preclinical evaluation of reinforcing and aversive properties of analgesics. In: Beers RF, Bassett EG (eds) Mechanics of pain and analgesic compounds. Raven, New York, pp 447–466

Hoffmeister F (1988) A comparison of the stimulus effects of codeine in rhesus monkeys under the contingencies of a two lever discrimination task and a cross self-administration paradigm: tests of generalization to pentazocine, buprenorphine, tilidine, and different doses of codeine. Psychopharmacology 94:315–320

Holtzman SG (1983) Discriminative stimulus properties of opioid agonists and antagonists. In: Cooper SJ (ed) Theory in psychopharmacology, vol 2. Academic, London, p 145

Holtzman SG (1990) Discriminative stimulus effects of drugs: relationship to potential for abuse. In: Adler MW, Cowan A (eds) Testing and evaluation of drugs of abuse, vol 6, Modern methods in pharmacology. Wiley-Liss, New York, pp 193–210

Jarbe TU, Swedberg MD (1998) Discriminative stimulus functions of CNS sedative drugs assessed by drug versus drug discrimination procedures in gerbils. Psychopharmacology 135:201–212

Kornetsky C, Bain B (1990) Brain-stimulation reward: a model for drug-induced euphoria. In: Adler MW, Cowan A (eds) Testing and evaluation of drugs of abuse, vol 6, Modern methods in pharmacology. Wiley-Liss, New York, pp 211–231

Lal H, Sherman GT (1980) Interceptive discriminative stimuli in the development of CNS drugs and a case of an animal model of anxiety. Annu Rep Med Chem 15:51–58

Littmann K, Heredia JM, Hoffmeister F (1979) Eine neue Methode zur enteralen Verabreichung von psychotrop wirksamen Substanzen beim Rhesusaffen. Arzneim Forsch/ Drug Res 29:1888–1890

Locke KW, Gorney B, Cornfeldt M, Fielding S (1991) Comparison of the stimulus effects of ethylketocyclazocine in Fischer and Sprague–Dawley rats. Drug Dev Res 23:65–73

Marcus R, Kornetsky C (1974) Negative and positive intracranial thresholds: effects of morphine. Psychopharmacologia 38:1–13

McMillan DE, Wessinger WD, Li M (2009) Effects of drugs and drug combination in pigeons trained to discriminate among pentobarbital, dizocilpine, a combination of these drugs, and saline. J Exp Anal Behav 92:387–412

Meert TF, Janssen PAJ (1989) Psychopharmacology of ritanserin: comparison with chlordiazepoxide. Drug Dev Res 18:119–144

Meert TF, de Haes P, Janssen PAJ (1989) Risperidone (R 64 766), a potent and complete LSD antagonist in drug discrimination by rats. Psychopharmacology 97:206–212

Meert TF, de Haes LAJ, Vermote PCM, Janssen PAJ (1990) Pharmacological validation of ritanserin and risperidone in the drug discrimination procedure in the rat. Drug Dev Res 19:353–373

Meisch RA, Carroll ME (1987) Oral drug self-administration: drugs as reinforcers. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 143–160

Olds J (1979) Drives and reinforcements: behavioral studies of hypothalamic functions. Raven, New York

Olds J, Killam KF, Bachy-Rita P (1956) Self-stimulation of the brain used as screening method for tranquilizing drugs. Science 124:265–266

Overton DA (1987) Applications and limitations of the drug discrimination method for the study of drug abuse. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 291–340

Porsolt RD, Castagné V, Dürmüller N, Lemaire M, Moser P, Roux S, France Central nervous system (CNS) safety pharmacology studies

Shannon HE, Holtzman SG (1976) Evaluation of the discriminative effects of morphine in the rat. J Pharmacol Exp Ther 198:64–65

Shannon HE, Holtzman SG (1986) Blockade of the discriminative effects of morphine by naltrexone and naloxone. Psychopharmacologia 50:119–124

Shelton KL, Dukat M, Allan AM (2004) Effects of 5-HT_3 receptor over-expression on the discriminative stimulus effects of ethanol. Alcohol Clin Exp Res 28:1161–1171

Sherman G, Lal H (1979) Discriminative stimulus properties of pentylenetetrazol and begrimide: some generalization and antagonism tests. Psychopharmacology 64:315–319

Sherman GT, Lal H (1980) Generalization and antagonism studies with convulsant, GABAergic and anticonvulsant drugs in rats trained to discriminate pentylenetetrazol from saline. Neuropharmacol 19:473–479

Sherman GT, Miksic S, Lal H (1979) Lack of tolerance development to benzodiazepines in antagonism of the pentylenetetrazol discriminative stimulus. Pharmacol Biochem Behav 10:795–797

Stewart JL, McMahon LR (2010) Rimonabant-induced delta9-tetrahydrocannabinol withdrawal in rhesus monkeys: discriminative stimulus effects and other withdrawal signs. J Pharmacol Exp Ther 334:347–356

Stolerman IP, Chamberlain S, Bizarro L, Fernandes C, Schalkwyk L (2004) The role of nicotinic receptor alpha 7 subunits in nicotine discrimination. Neuropharmacology 46:363–371

Stolerman IP, Mariathasan EA, White JA, Olufsen KS (1999) Drug mixtures and ethanol as compound internal stimuli. Pharmacol Biochem Behav 64:221–228

van Heest A, Hijzen TH, Slangen JL, Oliver B (1992) Assessment of the stimulus properties of anxiolytic drugs by means of the conditioned taste aversion procedure. Pharmacol Biochem Behav 42:487–495

Weeks JR, Collins RJ (1987) Screening for drug reinforcement using intravenous self-administration in the rat. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 35–43

Woods JH, France CP, Winger G, Bertamio AJ, Schwarz-Stevens K (1993) Opioid abuse liability assessment in rhesus monkeys. In: Herz A, Akil H, Simon EJ (eds) Opioids II, vol 104, Handbook of experimental pharmacology. Springer, Berlin/Heidelberg/New York, pp 609–632, chapter 55

Woolverton WL, Nader MA (1990) Experimental evaluation of the reinforcing effects of drugs. In: Adler MW, Cowan A (eds) Testing and evaluation of drugs of abuse, vol 6, Modern methods in pharmacology. Wiley-Liss, New York, pp 165–192

Woolverton WL, Schuster CL (1983) Intragastric self-administration in rhesus monkeys under limited access conditions: Methodological studies. J Pharmacol Methods 10:93–106

Yokel RA (1987) Intravenous self-administration: response rates, the effects of pharmacological challenges, and drug preference. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/ Berlin/Heidelberg, pp 1–33

10.1.4.3 Self-Administration Studies

PURPOSE AND RATIONALE

Drug self-administration is studied under a variety of conditions that can involve free or limited access. Some procedures (e.g., two-bottle choice for alcohol drinking in rodents) provide conditions that promote voluntary drug intake without particular attention to patterns of drug taking whereas other procedures (e.g., operant self-administration) permit detailed examination of specific aspects of drug taking. Operant procedures involving i.v. drug administration are the most widely used procedures for assessing abuse liability, and these procedures have a high degree of predictive validity for drugs that are abused by humans. The goal of self-administration procedures is often to compare self-administration of a test substance to self-administration of a standard reference substance and known drug of abuse (e.g., heroin). Alternatively, other procedures test whether drug naïve animals will initiate and maintain self-administration of a test substance.

PROCEDURE

Self-administration procedures in rodents commonly use the i.v. route of drug administration as this route maximizes the likelihood of detecting positive reinforcing effects because of the rapid onset of drug action after i.v. administration. Unlike drug discrimination and conditioned place preference procedures, where onset and duration of drug action are not critical factors so long as drugs are studied at times (and doses) that have activity, pharmacokinetics are critically important for self-administration studies. Even drugs that otherwise are very effective, positive reinforcers can be less effective or ineffective when their administration is delayed after a response. Self-administration procedures also are available for oral, intragastric, parenteral, and inhalation routes of administration.

Male Sprague–Dawley rats weighing 250–300 g are used for these studies. The apparatus consists of commercially available operant chambers equipped with levers, lights, a food hopper, and a mechanism for i.v. drug delivery (e.g., syringe pump).

Food-restricted rats are first trained to press levers for food prior to catheter implantation; the useful period of the catheter is extended when rats are trained to press levers for food before surgery. In daily sessions, a single response on either lever delivers a food pellet. After a single session in which 50 pellets are received under the continuous reinforcement schedule, one of the levers is designated (randomly or systematically balanced across subjects in a group) the active lever for the remainder of the study. The response requirement is increased over days, so long as rats receive the maximum of 50 pellets in a session, to a maximum of 5 (fixed-ratio [FR] 5). Once responding is reliable under the FR 5 schedule (e.g., 50 pellets delivered per session for three consecutive sessions), food training is suspended and the rats receive a chronic indwelling catheter.

Surgery is conducted under isoflurane anesthesia with the catheter (3 French) implanted in the jugular or femoral vein. The catheter is tunneled s.c., exteriorized in the midscapular region, and connected to an access port that is mounted in a jacket. For daily 90-min sessions, a Huber point needle connected to a syringe pump by sterile tubing delivers drug or vehicle to the access port and catheter. The port and catheter are filled with heparinized saline after each session. The beginning of the self-administration session is signaled by illumination of lights over the active lever; five responses on the active lever deliver drug or vehicle with each injection followed by a 3-min timeout when the chamber is dark and lever presses have no programmed consequence.

Stable self-administration responding is established with a reference compound (e.g., 0.32 mg/kg/injection, cocaine, i.v.), defined by three consecutive sessions when the number of injections received per session is greater than 20 and the number of injections in each session does not vary by more than $\pm 20\%$ of the mean number of injections for those sessions. Next, saline is substituted for the reference compound in order to extinguish responding and, thereby, to confirm the positive reinforcing effects of the reference compound under these conditions. Extinction is defined as three consecutive sessions when the number of saline injections received per session is less than eight. Once these criteria are satisfied, a dose of test substance is substituted to see if it maintains self-administration responding. The test substance is studied for a minimum of five and a maximum of ten sessions or until stable responding is observed, as defined by three consecutive sessions when the number of injections received per session does not vary by more than $\pm 20\%$ of the mean number of injections for those sessions. Following the test substance, saline is

available for self-administration for a minimum of five sessions and until the number of saline injections received is less than eight for three consecutive sessions. Finally, a retest with the reference substance (e.g., cocaine) confirms the sensitivity of the assay (and the subject) to positive reinforcing effects of a known drug of abuse. Different doses of a test substance are studied in different groups (n = 8/group) of rats that are initially trained to self-administer a reference substance.

EVALUATION

Self-administration of a test substance is compared to self-administration of vehicle and self-administration of the reference substance. Data are expressed either as the number of injections (mean ± SEM) received per session or as the response rate on the active lever. A range of doses of the test substance must be examined in order to insure that sufficient exposure occurred to test whether that substance has positive reinforcing effects.

CRITICAL ASSESSMENT OF THE METHOD

Self-administration procedures are, generally, not pharmacologically specific insofar as animals with a history of self-administering a drug from one pharmacological class (e.g., cocaine-like stimulant) will readily self-administer a drug from a different pharmacological class (e.g., heroin-like opioid), although there are examples where specific drug and behavioral history can facilitate subsequent drug self-administration (Collins and Woods 2009). While the predicative validity of self-administration studies in nonhumans is quite high for abuse liability in humans, it is not unanimous insofar as some drugs that are abused by humans (e.g., lysergic acid dimethylamide) are not readily self-administered by nonhumans. Conversely, some drugs that are self-administered by nonhumans do not appear to have high-abuse liability in humans (e.g., modafinil). Nevertheless, i.v. self-administration procedures remain the "gold standard" in preclinical studies for assessing and predicting abuse liability.

MODIFICATIONS OF THE METHOD

In addition to fixed-ratio schedules, a variety of different schedules of reinforcement have been used to study drug reinforcement including second-order schedules (Howell et al. 2007), multiple schedules (Ginsburg and Lamb 2006), and progressive ratio schedules (Carroll et al. 2011).

Winsauer et al. (2000) examined the effects of self-administered cocaine on acquisition and performance of response sequences for food using a multiple schedule in monkeys.

Henry and Howell (2009) studied reinstatement of responding by non-contingent i.v. cocaine injections in monkeys with a history of i.v. cocaine self-administration under a second-order schedule.

Wang and Woolverton (2007) used progressive ratio schedules to compare reinforcing effects of the isomers of MDMA and of methamphetamine in monkeys.

Modification by amphetamine of the reinforcing effects of cocaine under a progressive ratio schedule was studied in rats (Chiodo et al. 2008) and rhesus monkeys (Czoty et al. 2010).

Responding that has been extinguished (by responding in the absence of drug or the absence of drug and drug-paired stimuli) can be reinstated by presenting various stimuli, including drugs, non-drug stimuli that were paired with contingent drug administration, or by stress. Such reinstatement procedures are used to examine, in the preclinical laboratory (Bossert et al. 2007; Holtz et al. 2011), some of the factors that might contribute to reinitiation of drug taking in abstinent individuals.

Extending the period of drug access in self-administration procedures increases drug intake more than the proportional increase in session length (Ahmed et al. 2000) and can modify sensitivity to drugs (Morgan and Roberts 2004) as well as increase the likelihood of dependence developing (O'Dell et al. 2007).

References and Further Reading

Ahmed SH, Walker JR, Koob GE (2000) Persistent increase in the motivation to take heroin in rats with a history of drug escalation. Neuropsychopharmacology 22:413–421

Bossert JM, Poles GC, Wihbey KA, Koya E, Shaham Y (2007) Differential effects of blockade of dopamine D1-family receptors in nucleus accumbens core or shell on reinstatement of heroin seeking induced by contextual and discrete cues. J Neurosci 27:12655–12663

Carroll ME, Gao Y, Brimijoin S, Anker JJ (2011) Effects of cocaine hydrolase on cocaine self-administration under a PR schedule and during extended access (escalation) in rats. Psychopharmacology 213:817–829

Chiodo KA, Läck CM, Roberts DC (2008) Cocaine self-administration reinforced on a progressive ratio schedule decreases with continuous D-amphetamine treatment in rats. Psychopharmacology 200:465–473
Collins GT, Woods JH (2009) Influence of conditioned reinforcement on the response-maintaining effects of quinpirole in rats. Behav Pharmacol 20:492–504
Czoty PW, Martelle JL, Nader MA (2010) Effects of chronic d-amphetamine administration on the reinforcing strength of cocaine in rhesus monkeys. Psychopharmacology 209: 375–382
Ginsburg BC, Lamb RJ (2006) Fluvoxamine effects on concurrent ethanol- and food-maintained behaviors. Exp Clin Psychopharmacol 14:483–492
Henry PK, Howell LL (2009) Cocaine-induced reinstatement during limited and extended drug access conditions in rhesus monkeys. Psychopharmacology 204:523–529
Holtz NA, Lozama A, Prisinzano TE, Carroll ME (2011) Reinstatement of methamphetamine seeking in male and female rats treated with modafinil and allopregnanoloneDrug Alcohol Depend (Epub ahead of print) PMID:21820819
Howell LL, Carroll FI, Votaw JR, Goodman MM, Kimmel HL (2007) Effects of combined dopamine and serotonin transported inhibitors on cocaine self-administration in rhesus monkeys. J Pharmacol Exp The 320:757–765
Morgan D, Roberts DC (2004) Sensitization to the reinforcing effects of cocaine following binge-abstinent self-administration. Neurosci Biobehav Rev 27:803–812
O'Dell LE, Chen SA, Smith RT, Specio SE, Balster RL, Paterson NE, Markou A, Zorilla EP, Koob GF (2007) Extended access to nicotine self-administration leads to dependence: circadian measures, withdrawal measures, and extinction behavior in rats. J Pharmacol Exp Ther 320:180–193
Wang Z, Woolverton WL (2007) Estimating the relative reinforcing strength of (+/−)-3,4-methylenedioxymethamphetamine (MDMA) and its isomers in rhesus monkeys: comparison to (+)-methamphetamine. Psychopharmacology 189: 483–488
Winsauer PJ, Silvester KR, Moerschbaecher JM, France CP (2000) Cocaine self-administration in monkeys: effects on the acquisition and performance of response sequences. Drug Alcohol Depend 59:51–61

10.1.4.4 Conditioned Place Preference Studies

PURPOSE AND RATIONALE

Conditioned place preference procedures have been used to examine behavioral actions that are thought to be related to positive reinforcing effects as measured by other procedures, such as self-administration (van der Kooy 1987; Hoffman 1998; Tzschenke 1998; Self and Stein 1992). Particular environmental stimuli are paired with the presence or absence of a presumed reinforcer (e.g., drug or food), and later, in the absence of that reinforcer, animals are tested for their preference for either environment.

PROCEDURE

To induce place preference with food, a food-restricted animal is exposed to an experimental chamber that consists of two compartments (which differ in floor texture and/or wall color) and that are separated by a removable barrier. In some iterations of this procedure, the two compartments are joined by a small tunnel or a third (neutral) compartment. On alternate days, the animal is confined to one or the other compartment, with food available in only one of the compartments. Thus, food is selectively paired with one of the distinctive environments. After several (e.g., four in each compartment for a total of eight) conditioning sessions, the animal is placed in the same chamber without the barrier in place (for procedures that use a third [neutral] compartment, the animal is placed in that compartment and otherwise in the middle of the chamber). In the absence of the reinforcer (e.g., food), animals demonstrate a relative increase in the amount of time spent in the environment that was paired with the reinforcer (e.g., food) as compared to the compartment that was not paired with the reinforcer. Place conditioning with drugs is conceptually similar and involves the differential pairing of drug effect with one compartment and the absence of drug effect (vehicle) with the other. Drugs can be administered by various different routes (Amalric et al. 1987, Bals-Kubik et al. 1990; Iwamoto 1988; Shippenberg and Herz 1987), and usually animals are placed in the chamber immediately after drug administration for a 40-min conditioning session.

Male Sprague–Dawley rats weighing 250–300 g are typically used for these studies. Drugs are usually administered i.p. or s.c. When drugs are to be administered intracerebroventricularly, rats are anesthetized with 60 mg/kg i.p. sodium hexobarbital and 23-gauge guide cannulae aimed at the lateral ventricle ($AP = -0.9$ mm, $L = +1.5$ mm, $DV = 3.5$ mm) (Paxinos and Watson 1982) are stereotaxically implanted; conditioning commences 1 week later.

The apparatus consists of $30 \times 60 \times 30$-cm Plexiglas boxes. For conditioning sessions, each box is divided into two equal-sized compartments by means of a removable sliding wall. One compartment is white with a textured floor, the other black with a smooth floor. For testing, the central wall is raised 12 cm above the floor to allow passage from one compartment to the other.

Conditioning sessions are conducted once a day for 8 days and consist of administering drug or its vehicle

on alternate days. The rats are immediately confined to one compartment of the box following drug injection and to the other compartment following vehicle injection. Conditioning sessions last 40 min although, for drugs with delayed onset or very short duration of action, the temporal conditions need to be adjusted to insure that conditioning occurs at a time of biological activity. Test sessions are carried out 1 day after the last training session and in the absence of drug. The rats are placed in a neutral position (either in the center or in the neutral compartment) of the test box and allowed free access to both sides of the box for 15 min. A video camera with integrated stopwatch is used for data recording. Alternatively, photocells mounted along the sides of each compartment can be used to electronically monitor the location of the subject in the apparatus. The time spent in each compartment is assessed by visual analysis of the recorded videotape or by data collected through photocell beam breaks.

For intracerebroventricular injections, a 30-gauge injection needle is attached to a microsyringe via polyethylene tubing. The drug solutions are administered over a 60-s period, and the injection needles are left in place for an additional 30 s to ensure complete delivery of the solution. For antagonism tests, groups of rats receive an intracerebroventricularly injection of the antagonist (naltrexone or naloxone) or vehicle 10 min before the microinjection of the conditioning drug. At the end of the experiments, the rats are anesthetized and sacrificed by decapitation. The brains are removed and sectioned in a cryostat to verify the location of the cannulae. Alternatively, antagonists can be administered systemically.

EVALUATION

Conditioning scores represent the time spent in the drug-paired place minus the time spent in the vehicle-paired place and are expressed as means ± SEM. In cases where animals show a bias toward one compartment prior to conditioning, drug conditioning can be established with the non-preferred compartment, thereby increasing the confidence that preference for that compartment is specifically related to drug administration. A range of doses should be studied since the dose–response curve for conditioned place preference can be biphasic such that smaller doses produce preference whereas larger doses have no effect or produce an aversion.

CRITICAL ASSESSMENT OF THE METHOD

Conditioned place preference procedures are not pharmacologically selective in the manner that drug discrimination studies are insofar as drugs from several different classes (e.g., opioids, ethanol, and stimulants) can generate positive results. Generally, there is a strong positive correlation between drugs that can be used to establish conditioned place preference and those that are positive reinforcers by other measures (e.g., i.v. self-administration); however, one of the most effective reinforcers in self-administration studies, that is also widely abused by humans, does not unanimously generate strong conditioned place preference in nonhumans—cocaine. Thus, results from conditioned place preference studies should be used in concert with results from other measures of reinforcing effects (e.g., self-administration) in order to determine the likelihood that a drug exerts a profile of behavioral effects that would indicate its abuse. For the purpose of opioids, in general, mu opioid receptor agonists are effective for establishing place preference whereas kappa receptor agonists are not. In fact, kappa receptor agonists can generate place aversion (e.g., Sante et al. 2000).

MODIFICATIONS OF THE METHOD

In order to distinguish place preference and place aversion, place-conditioning behavior can be expressed by a difference in the time spent in the preferred and the non-preferred sides in the postconditioning and preconditioning tests, respectively. Positive values indicate preference and negative values aversion (Kitaichi et al. 1996). For non-biased procedures, where animals do not show an inherent preference for either compartment, results are presented simply as a difference score (i.e., time spent in the drug-paired compartment minus time spent in the vehicle-paired compartment).

In addition to place preference, others (Mucha and Herz 1985; Broadbent et al. 2002) used taste preference conditioning.

Foltin and Evans (1997) established place preference for cocaine in rhesus monkeys, and Wang et al. (2011) established a preference with morphine in monkeys.

Cunningham (Bormann and Cunningham 1998; Gabriel et al. 2004) and others (Sevak et al. 2007, 2008a, b) use the same chamber for training and testing with the exception that only floor texture varies

according to treatment condition. Thus, drug and vehicle are paired with different floor textures, and during test sessions, the time spent on each section of a floor comprising the two different textures (half of the floor with each) is used as an index of preference or aversion. This procedure has the advantage that the size of the test chamber is not different from the size of the training chamber.

Perks and Clifton (1997) used sucrose solution to generate a place preference which was subsequently devalued using a LiCl taste aversion procedure.

Brockwell et al. (1996) described a computerized system for the simultaneous monitoring of place conditioning and locomotor activity in rats consisting of four independent conditioning boxes, each equipped with six pairs of photosensors connected to an Experiment Controller, an electronic board containing a microprocessor, a programmable timer, and 16 K of RAM used to store both instructions and data.

Steinpreis et al. (1996) investigated place preference in Sprague–Dawley rats treated with graded i.p. doses of methadone. Place preference for methadone peaked at 4 mg/kg, and aversion was produced at 10 mg/kg.

Using the conditioned place preference paradigm, Mamoon et al. (1995) assessed the rewarding properties of butorphanol in comparison to morphine after unilateral microinjections into the ventral tegmental area of male Lewis rats.

Gaiardi et al. (1997) assessed rewarding and aversive effects of buprenorphine by place preference and taste aversion conditioning. After s.c. administration of doses ranging from 0.025 to 0.1 mg/kg, buprenorphine caused a significant increase in the amount of time spent on the drug-paired compartment but no significant decrease of saccharin consumption. Rewarding and aversive effects did not occur within a similar dose range.

Contarino et al. (1997) found no tolerance to the rewarding properties of morphine, after repeated i.p. injections of morphine, in prolonged conditioned place preference trials.

Tsuji et al. (1996) studied the effect of microinjections of GABA receptor agonists and antagonists into the ventral tegmental area of Sprague Dawley rats on morphine-induced place preference.

Sufka (1994) recommended the conditioned place preference paradigm as a novel approach for assessing effects of opioids in chronic pain induced in rats by unilateral injections of Freund's adjuvant into the hind paw.

Conditioned place avoidance by naloxone was attenuated by clonidine (Kosten 1994).

In addition to morphine and other mu opioid receptor agonists, other drugs with known or putative abuse liability were tested in the place-conditioning paradigm including the following: cocaine (Lepore et al. 1995; Suzuki and Misawa 1995; Calcagnetti et al. 1996; Martin-Iverson and Reimer 1996; Martin-Iverson et al. 1997), caffeine (Brockwell et al. 1991; Brockwell and Beninger 1996), cannabinoids (Lepore et al. 1995; Sañudo-Peña et al. 1997), LSD (Parker 1996), methamphetamine (Suzuki and Misawa 1995), amphetamine (Hoffman and Donovan 1995; Turenne et al. 1996), methylphenidate (Gatley et al. 1996) and fenfluramine (Davies and Parker 1993), 7-OH-DPAT (Khroyan et al. 1995; Chaperon and Thiébot 1996), gamma-hydroxybutyric acid (Martellotta et al. 1997), propofol (Pain et al. 1997), alcohol (Kennedy et al. 2011; Voorhees and Cunningham 2011; Zarrindast et al. 2010), methylenedioxymethamphetamine (Daza-Losada et al. 2011), and NMDA receptor antagonists (Steinpreis et al. 1995; Papp et al. 1996).

Furthermore, 5-HT_3 receptor antagonists (Acquas et al. 1990), 5-HT_3 receptor agonists (Higgins et al. 1993), dopamine release inhibitors (Schechter and Meehan 1994), dopamine D1 receptor antagonists (Acquas and Di Chiara 1994), dopamine D3 receptor agonists (Khroyan et al. 1997), and antiemetic agents (Frisch et al. 1995) were studied in the place-conditioning paradigm.

Suzuki et al. (1991, 1993) and del Poso et al. (1996) studied opioid-induced place preference in mice, and Bechtholt et al. (2004) studied the effects of handling on conditioned place aversion and conditioned place preference by ethanol in mice.

References and Further Reading

Acquas E, Di Chiara G (1994) D1 receptor blockade stereospecifically impairs the acquisition of drug-conditioned place preference and place aversion. Behav Pharmacol 5:555–560

Acquas E, Carboni E, Garau L, Di Chiara G (1990) Blockade of acquisition of drug-conditioned place aversion by 5-HT_3 antagonists. Psychopharmacology 100:459–463

Amalric M, Cline EJ, Martinez JL Jr, Bloom FE, Koob GF (1987) Rewarding properties of β-endorphin as measured by conditioned place preference. Psychopharmacology 91:14–19

Bals-Kubik R, Herz A, Shippenberg TS (1988) β-endorphin-(1–27) is a naturally occurring antagonist of the reinforcing effects of opioids. Naunyn -Schmiedeberg's Arch Pharmacol 338:392–396

Bals-Kubik R, Shippenberg TS, Herz A (1990) Involvement of central μ and δ opioid receptors in mediating the reinforcing effects of beta-endorphin in the rat. Eur J Pharmacol 175:63–69

Bechara A, Van der Kooy D (1987) Kappa receptors mediate the peripheral aversive effects of opiates. Pharmacol Biochem Behav 28:227–233

Bechtholt AJ, Gremel CM, Cunningham CL (2004) Handling blocks expression of conditioned place aversion but not conditioned place preference by ethanol in mice. Pharmacol Biochem Behav 79:739–744

Bormann NM, Cunningham CL (1998) Ethanol-induced conditioned place aversion in rats: effects of interstimulus interval. Pharmacol Biochem Behav 59:427–432

Broadbent J, Muccino KJ, Cunningham CL (2002) Ethanol-induced conditioned taste aversion in 15 inbred mouse strains. Behav Neurosci 116:138–148

Brockwell NT, Beninger RJ (1996) The differential role of A1 and A2 adenosine subtypes in locomotor activity and place conditioning in rats. Behav Pharmacol 7:373–383

Brockwell NT, Eikelboom R, Beninger RJ (1991) Caffeine-induced place and taste conditioning: production of dose-dependent preference and aversion. Pharmacol Biochem Behav 38:513–517

Brockwell NT, Ferguson DS, Beninger RJ (1996) A computerized system for the simultaneous monitoring of place conditioning and locomotor activity in rats. J Neurosci Methods 64:227–232

Calcagnetti DJ, Quatrella LA, Schechter MD (1996) Olfactory bulbectomy disrupts the expression of cocaine-induced conditioned place preference. Physiol Behav 59:597–604

Chaperon F, Thiébot MH (1996) Effects of dopaminergic D3-receptor-preferring ligands on the acquisition of place conditioning in rats. Behav Pharmacol 7:105–109

Contarino A, Zanotti A, Drago F, Natolino F, Lipartiti M, Giusti P (1997) Conditioned place preference: no tolerance to the rewarding properties of morphine. Naunyn-Schmiedeberg's Arch Pharmacol 355:589–594

Davies AM, Parker LA (1993) Fenfluramine-induced place aversion in a three-choice apparatus. Pharmacol Biochem Behav 44:595–600

Daza-Losada M, Minarro J, Aguilar MA, Valverde O, Rodriguez-Arias M (2011) Acute blockade of CB1 receptor leads to reinstatement of MDMA-induced conditioned place preference. Pharmacol Biochem Behav 100:33–39

Del Poso E, Barrios M, Baeyens JM (1996) The NMDA receptor antagonist dizocilpine (MK-801) stereoselectively inhibits morphine-induced place preference in mice. Psychopharmacology 125:209–213

Foltin RW, Evans SM (1997) A novel procedure for studying food and drug seeking in rhesus monkeys. Psychopharmacology 132:209–216

Frisch C, Hasenöhrl RU, Mattern CM, Häcker R, Huston JP (1995) Blockade of lithium chloride-induced conditioned place aversion as a test for antiemetic agents: comparison of metoclopramide with combined extracts of Zingiber officinale and Ginkgo biloba. Pharmacol Biochem Behav 52:321–327

Gabriel KI, Cunningham CL, Finn DA (2004) Allopregnanolone does not influence ethanol-induced conditioned place preference in DBA/2 J mice. Psychopharmacology 176:50–56

Gaiardi M, Bartoletti M, Bacchi A, Gubellini C, Babbibi M (1997) Motivational properties of buprenorphine as assessed by place and taste conditioning in rats. Psychopharmacology 130:104–108

Gatley SJ, Meehan SM, Chen R, Pan D-F, Schechter MD, Dewey SL (1996) Place preference and microdialysis studies with two derivatives of methylphenidate. Life Sci 58:PL 345–PL 352

Higgins GA, Joharchi N, Sellers EM (1993) Behavioral effects of the 5-hydroxytryptamine$_3$ receptor agonists 1-phenylbiguanide and m-chlorophenylbiguanide in rats. J Pharmacol Exp Ther 264:1440–1449

Hoffman DC (1998) The use of place conditioning in studying the neuropharmacology of drug reinforcement. Brain Res Bull 23:373–387

Hoffman DC, Donovan H (1995) Effects of typical, atypical, and novel antipsychotic drugs on amphetamine-induced place conditioning in rats. Drug Dev Res 36:193–198

Iwamoto ET (1988) Dynorphin A (1–17) induces 'reward' in rats in the place conditioning paradigm. Life Sci 43:503–508

Kennedy BC, Panksepp JB, Runckel PA, Lahvis GP (2011) Social influences on morphine-conditioned place preference in adolescent BALB/cJ and C57BL/6J mice. Psychopharmacology (Epub ahead of print) PMID:21837434

Khroyan TV, Baker DA, Neisewander JL (1995) Dose-dependent effects of the D_3-preferring agonist 7-OH-DPAT on motor behaviors and place conditioning. Psychopharmacology 122:351–357

Khroyan TV, Fuchs RA, Baker DA, Neisewander JL (1997) Effects of D3-preferring agonists 7-OH-PIPAT and PD-128,907 on motor behaviors and place conditioning. Behav Pharmacol 8:65–74

Kitaichi K, Noda Y, Hasegawa T, Furukawa H, Nabeshima T (1996) Acute phencyclidine induces aversion, but repeated phencyclidine induces preference in the place conditioning test in rats. Eur J Pharmacol 318:7–9

Kosten TA (1994) Clonidine attenuates conditioned aversion produced by naloxone-precipitated opiate withdrawal. Eur J Pharmacol 254:59–63

Lepore M, Vorel SR, Lowinson J, Gardner EL (1995) Conditioned place preference induced by Δ^9-tetrahydrocannabinol: comparison with cocaine, morphine, and food award. Life Sci 56:2073–2080

Mamoon AM, Barnes AM, Ho IK, Hoskins B (1995) Comparative rewarding properties of morphine and butorphanol. Brain Res Bull 38:507–511

Martellotta MC, Fattore L, Cossu G, Fratta W (1997) Rewarding properties of gamma-hydroxybutyric acid: an evaluation through place preference paradigm. Psychopharmacology 132:1–5

Martin-Iverson MT, Reimer AR (1996) Classically conditioned motor effects do not occur with cocaine in an unbiased conditioned place preferences procedure. Behav Pharmacol 7:303–314

Martin-Iverson MT, Reimer AR, Sharma S (1997) Unbiased cocaine conditioned place preferences (CPP) obscures conditioned locomotion, and nimodipine blockade of cocaine CPP is due to conditioned place aversions. Psychopharmacology 130:327–333

Mucha RF, Herz A (1985) Motivational properties of kappa and mu-opioid agonists studied with place and taste preference conditioning procedures. Psychopharmacology 82:241–245

Mucha RF, Iversen SD (1984) Reinforcing properties of morphine and naloxone revealed by conditioned place preferences: a procedural examination. Psychopharmacology 82:241–247

Pain L, Oberling P, Sandner G, Di Scala G (1997) Effect of midazolam on propofol-induced positive affective state assessed by place conditioning in rats. Anesthesiology 87:935–943

Papp M, Moryl E, Maccechini ML (1996) Differential effects of agents acting at various sites of the NMDA receptor complex in a place preference conditioning model. Eur J Pharmacol 317:191–196

Parker LA (1996) LSD produces place preference and flavor avoidance but does not produce flavor aversion in rats. Behav Neurosci 110:503–508

Paxinos G, Watson C (1982) The rat in stereotaxic coordinates. Academic, Sidney

Perks SM, Clifton PG (1997) Reinforcer revaluation and conditioned place preference. Physiol Behav 61:1–5

Sante AB, Nobre MJ, Brandao ML (2000) Place aversion induced by blockade of mu or activation of kappa opioid receptors in the dorsal periaqueductal gray matter. Behav Pharmacol 11:583–589

Sañudo-Peña CM, Tsou K, Delay ER, Hohman AG, Force M, Walker JM (1997) Endogenous cannabinoids as an aversive or counter-rewarding system in the rat. Neurosci Lett 223:125–128

Schechter MD, Meehan SM (1994) Conditioned place aversion produced by dopamine release inhibition. Eur J Pharmacol 260:133–137

Self DW, Stein L (1992) Receptor subtypes in opioid and stimulation reward. Pharmacol Toxicol 70:87–94

Sevak RJ, Koek W, Daws LC, Owens WA, Galli A, France CP (2008a) Behavioral effects of amphetamine in streptozotocin-treated rats. Eur J Pharmacol 581:105–112

Sevak RJ, Koek W, Owens WA, Galli A, Daws LC, France CP (2008b) Feeding conditions differentially affect the neurochemical and behavioral effects of dopaminergic drugs in male rats. Eur J Pharmacol 592:109–115

Sevak RJ, Owens WA, Koek W, Galli A, Daws LC, France CP (2007) Evidence for D2 receptor mediation of amphetamine-induced normalization of locomotion and dopamine transporter function in hypoinsulinemic rats. J Neurochem 101:151–159

Shippenberg TS, Herz A (1987) Place preference conditioning reveals the involvement of D_1-dopamine receptors in the motivational properties of mu and kappa opioid agonists. Brain Res 436:169–172

Shippenberg TS, Bals-Kubik R, Herz A (1987) Motivational properties of opioids: evidence that an activation of δ-receptors mediate reinforcement processes. Brain Res 436: 234–239

Steinpreis RE, Kramer MA, Mix KS, Piwowarczyk MC (1995) The effects of MK801 on place conditioning. Neurosci Res 22:427–430

Steinpreis RE, Rutell AL, Parrett FA (1996) Methadone produces conditioned place preference in the rat. Pharmacol Biochem Behav 54:339–431

Sufka KJ (1994) Conditioned place preference paradigm: a novel approach for analgesic drug assessment against chronic pain. Pain 58:355–366

Suzuki T, Misawa M (1995) Sertindole antagonizes morphine-, cocaine-, and methamphetamine-induced place preference in the rat. Life Sci 57:1277–1284

Suzuki T, Funada M, Narita M, Misawa M, Nagase H (1991) Pertussis toxin abolishes μ and δ opioid agonist-induced place preference. Eur J Pharmacol 205:85–88

Suzuki T, Funada M, Narita M, Misawa M, Nagase H (1993) Morphine-induced place preference in the CXBK mouse: characteristics of μ opioid receptor subtypes. Brain Res 602:45–52

Tsuji M, Nakagawa Y, Ishibashi Y, Yoshii T, Takashima T, Shimada M, Suzuki T (1996) Activation of ventral tegmental $GABA_B$ receptors inhibits morphine-induced place preference in rats. Eur J Pharmacol 313:169–173

Turenne SD, Miles C, Parker LA, Siegel S (1996) Individual differences in reactivity to the rewarding/aversive properties of drugs: assessment by taste and place conditioning. Pharmacol Biochem Behav 53:511–516

Tzschenke M (1998) Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. Prog Neurobiol 56:613–6672

Van der Kooy D (1987) Place conditioning: a simple and effective method for assessing the motivational properties of drugs. In: Bozarth MA (ed) Methods of assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 229–240

Voorhees CM, Cunningham CL (2011) Involvement of the orexin/hypocretin system in ethanol conditioned place preference. Psychopharmacology 214:805–818

Wang JH, Wu XJ, Li CY, Wei JK, Jiang JJ, Liu CR, Yu CY, Carlson S, Hu XT, Ma H, Duan W, Ma YY (2011) Effect of morphine on conditioned place preference in rhesus monkeys. Addict Biol (Epub ahead or print) PMID:21305991

Zarrindast MR, Meshkani J, Rezayof A, Rotami P (2010) Nicotinic acetylcholine receptors of the dorsal hippocampus and the basolateral amygdala are involved in ethanol-induced conditioned place preference. Neuroscience 168:505–513

References and Further Reading

Aceto MD (1990) Assessment of physical dependence techniques for the evaluation of abused drugs. In: Adler MW, Cowan A (eds) Testing and evaluation of drugs of abuse, vol 6, Modern methods in pharmacology. Wiley-Liss, New York, pp 67–79

Acquas E, Di Chiara G (1994) D1 receptor blockade stereospecifically impairs the acquisition of drug-conditioned place preference and place aversion. Behav Pharmacol 5:555–560

Acquas E, Carboni E, Garau L, Di Chiara G (1990) Blockade of acquisition of drug-conditioned place aversion by $5\text{-}HT_3$ antagonists. Psychopharmacology 100:459–463

Ahmed SH, Walker JR, Koob GE (2000) Persistent increase in the motivation to take heroin in rats with a history of drug escalation. Neuropsychopharmacology 22:413–421

Amalric M, Cline EJ, Martinez JL Jr, Bloom FE, Koob GF (1987) Rewarding properties of β-endorphin as measured by conditioned place preference. Psychopharmacology 91:14–19

Bals-Kubik R, Herz A, Shippenberg TS (1988) β-endorphin-(1–27) is a naturally occurring antagonist of the reinforcing effects of opioids. Naunyn -Schmiedeberg's Arch Pharmacol 338:392–396

Bals-Kubik R, Shippenberg TS, Herz A (1990) Involvement of central μ and δ opioid receptors in mediating the reinforcing effects of beta-endorphin in the rat. Eur J Pharmacol 175:63–69

Balster RL, Prescott WR (1990) Δ^9-Tetrahydrocannabinol discrimination in rats as a model for cannabis intoxication. Neurosci Biobehav Rev 16:55–62

Bechara A, Van der Kooy D (1987) Kappa receptors mediate the peripheral aversive effects of opiates. Pharmacol Biochem Behav 28:227–233

Bechtholt AJ, Gremel CM, Cunningham CL (2004) Handling blocks expression of conditioned place aversion but not conditioned place preference by ethanol in mice. Pharmacol Biochem Behav 79:739–744

Becker GL, Gerak LR, Koek W, France CP (2008) Antagonist-precipitated and discontinuation-induced withdrawal in morphine-dependent rhesus monkeys. Psychopharmacology 201:373–382

Becker GL, Gerak LR, Li JX, Koek W, France CP (2010) Precipitated and conditioned withdrawal in morphine-treated rats. Psychopharmacology 209:85–94

Bertalmio AJ, Woods JH (1987) Differentiation between μ and κ receptor mediated effects in opioid drug discrimination: apparent pA_2 analysis. J Pharmacol Exp Ther 243:591–598

Bertalmio AJ, Herling S, Hampton RY, Winger G, Woods JH (1982) A procedure for rapid evaluation of the discriminative stimulus effects of drugs. J Pharmacol Methods 7:289–299

Black K, Shea C, Dursun S, Kutcher S (2000) Selective serotonin reuptake inhibitor discontinuation syndrome: proposed diagnostic criteria. J Psychiatry Neurosci 25:255–261

Boisse NR, Periana RM, Guarino JJ, Druger HS, Samoriski GM (1986) Pharmacologic characterization of acute chlordiazepoxide dependence in the rat. J Pharmacol Exp Ther 239:775–783

Boisse NR, Quaglietta N, Samoriski GM, Guarino JJ (1990) Tolerance and physical dependence to a short-acting benzodiazepine, midazolam. J Pharmacol Exp Ther 252:1125–1133

Bormann NM, Cunningham CL (1998) Ethanol-induced conditioned place aversion in rats: effects of interstimulus interval. Pharmacol Biochem Behav 59:427–432

Bossert JM, Poles GC, Wihbey KA, Koya E, Shaham Y (2007) Differential effects of blockade of dopamine D1-family receptors in nucleus accumbens core or shell on reinstatement of heroin seeking induced by contextual and discrete cues. J Neurosci 27:12655–12663

Bozarth MA (1987) Intracranial self-administration procedures for the assessment of drug reinforcement. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 178–187

Brady JV, Griffiths RR, Hienz RD, Ator NA, Lukas SE, Lamb RJ (1987) Assessing drugs for abuse liability and dependence potential in laboratory primates. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 45–85

Brandt MR, France CP (1998) Chronic l-alpha acetylmethadol in rhesus monkeys: discriminative stimulus and other behavioral measures of dependence and withdrawal. J Pharmacol Exp Ther 287:1029–1037

Broadbent J, Muccino KJ, Cunningham CL (2002) Ethanol-induced conditioned taste aversion in 15 inbred mouse strains. Behav Neurosci 116:138–148

Brockwell NT, Beninger RJ (1996) The differential role of A1 and A2 adenosine subtypes in locomotor activity and place conditioning in rats. Behav Pharmacol 7:373–383

Brockwell NT, Eikelboom R, Beninger RJ (1991) Caffeine-induced place and taste conditioning: production of dose-dependent preference and aversion. Pharmacol Biochem Behav 38:513–517

Brockwell NT, Ferguson DS, Beninger RJ (1996) A computerized system for the simultaneous monitoring of place conditioning and locomotor activity in rats. J Neurosci Methods 64:227–232

Buckett WR (1964) A new test for morphine-like physical dependence (addiction liability) in rats. Psychopharmacologia 6:410–416

Calcagnetti DJ, Quatrella LA, Schechter MD (1996) Olfactory bulbectomy disrupts the expression of cocaine-induced conditioned place preference. Physiol Behav 59:597–604

Carboni E, Acquas E, Leone P, di Chiara G (1989) 5-HT_3 receptor antagonists block morphine- and nicotine- but not amphetamine-induced award. Psychopharmacology 97:175–178

Carroll ME, Gao Y, Brimijoin S, Anker JJ (2011) Effects of cocaine hydrolase on cocaine self-administration under a PR schedule and during extended access (escalation) in rats. Psychopharmacology 213:817–829

Chaperon F, Thiébot MH (1996) Effects of dopaminergic D3-receptor-preferring ligands on the acquisition of place conditioning in rats. Behav Pharmacol 7:105–109

Chiodo KA, Läck CM, Roberts DC (2008) Cocaine self-administration reinforced on a progressive ratio schedule decreases with continuous D-amphetamine treatment in rats. Psychopharmacology 200:465–473

Collier HOJ, Cuthbert NJ, Francis DL (1981) Clonidine dependence in the guinea-pig isolated ileum. Br J Pharmacol 73:443–453

Collins GT, Woods JH (2009) Influence of conditioned reinforcement on the response-maintaining effects of quinpirole in rats. Behav Pharmacol 20:492–504

Colpaert FC (1987) Drug discrimination: methods of manipulation, measurement, and analysis. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 341–372

Colpaert FC, Janssen PAJ (1984) Agonist and antagonist effects of prototype opiate drugs in rats discrimination fentanyl from saline: Characteristics of partial generalization. J Pharmacol Exp Ther 220:193–199

Contarino A, Zanotti A, Drago F, Natolino F, Lipartiti M, Giusti P (1997) Conditioned place preference: no tolerance to the rewarding properties of morphine. Naunyn-Schmiedeberg's Arch Pharmacol 355:589–594

Cowan A, Zhu XZ, Mosberg HI, Omnaas JR, Porreca F (1988) Direct dependence studies in rats with agents selective for different types of opioid receptor. J Pharmacol Exp Ther 246:950–955

Cruz SL, Salazar LA, Villarreal JE (1991) A methodological basis for improving the reliability of measurements of opiate abstinence responses in the guinea pig ileum made dependent in vitro. J Pharmacol Methods 25:329–342

Czoty PW, Martelle JL, Nader MA (2010) Effects of chronic d-amphetamine administration on the reinforcing strength of cocaine in rhesus monkeys. Psychopharmacology 209:375–382

Davies AM, Parker LA (1993) Fenfluramine-induced place aversion in a three-choice apparatus. Pharmacol Biochem Behav 44:595–600

Davis CM, Stevenson GW, Cañadas F, Ullrich R, Rice KC, Riley AL (2009) Discriminative stimulus properties of naloxone in Long-Evans rats: assessment with the conditioned taste aversion baseline of drug discrimination learning. Psychopharmacology 209:421–429

Daza-Losada M, Minarro J, Aguilar MA, Valverde O, Rodriguez-Arias M (2011) Acute blockade of CB1 receptor leads to reinstatement of MDMA-induced conditioned place preference. Pharmacol Biochem Behav 100:33–39

Del Poso E, Barrios M, Baeyens JM (1996) The NMDA receptor antagonist dizocilpine (MK-801) stereoselectively inhibits morphine-induced place preference in mice. Psychopharmacology 125:209–213

Deneau GA (1964) Pharmacological techniques for evaluating addiction liability of drugs. In: Nodine JH, Siegler PE (eds) Animal and clinical pharmacologic techniques in drug evaluation. Year Book Medical Publishers., Chicago, pp 406–410

Deneau GA, Seevers MH (1964) Drug dependence. In: Laurence DR, Bacharach AL (eds) Evaluation of drug activities: pharmacometrics. Academic, London/New York, pp 167–179

Deneau G, Yanagita T, Seevers MH (1969) Self-administration of psychoactive substances by the monkey. Psychopharmacologia 16:30–48

Dykstra LA, Gmerek DE, Winger G, Woods JH (1987) Kappa opioids in rhesus monkeys. I. Diuresis, sedation, analgesia and discriminative stimulus effects. J Pharmacol Exp Ther 242:413–420

Dykstra LA, Bertalmio AJ, Woods JH (1988) Discriminative and analgesic effects of mu and kappa opioids: in vivo pA_2 analysis. In: Colpaert FC, Balster RL (eds) Transduction mechanisms of drug stimuli. Springer, Berlin/Heidelberg/New York, pp 107–121, Psychopharmacology series 4

Eppilito AK, Gerak LR (2010) Tolerance to the rate-increasing and not rate-decreasing effects of pregnenolone in rats. Behav Pharmacol (Epub ahead of print) PMID:20859199

Foltin RW, Evans SM (1997) A novel procedure for studying food and drug seeking in rhesus monkeys. Psychopharmacology 132:209–216

France CP (1995) A sensitive, efficient drug discrimination procedure for studying *kappa* antagonists in rhesus monkeys. Analgesia 1:421–424

France CP, Woods JH (1993) U-50488, saline, naltrexone discrimination in U-50,488 treated pigeons. Behav Pharmacol 4:509–516

France CP, Medzihradsky F, Woods JH (1994) Comparison of *kappa* opioids in rhesus monkeys: behavioral effects and binding affinities. J Pharmacol Exp Ther 268:47–58

France CP, Gerak LR, Winger GD, Medzihradsky F, Bagley JR, Brockunier LL, Woods JH (1995) Behavioral effects and receptor binding affinities of fentanyl derivatives in rhesus monkeys. J Pharmacol Exp Ther 274:17–28

Frisch C, Hasenöhrl RU, Mattern CM, Häcker R, Huston JP (1995) Blockade of lithium chloride-induced conditioned place aversion as a test for antiemetic agents: comparison of metoclopramide with combined extracts of Zingiber officinale and Ginkgo biloba. Pharmacol Biochem Behav 52:321–327

Gabriel KI, Cunningham CL, Finn DA (2004) Allopregnanolone does not influence ethanol-induced conditioned place preference in DBA/2 J mice. Psychopharmacology 176:50–56

Gaiardi M, Bartoletti M, Bacchi A, Gubellini C, Babbibi M (1997) Motivational properties of buprenorphine as assessed by place and taste conditioning in rats. Psychopharmacology 130:104–108

Gallaher EJ, Henauer SA, Jacques CJ, Hollister LE (1986) Benzodiazepine dependence in mice after ingestion of drug-containing food pellets. J Pharmacol Exp Ther 237:462–467

Garcia J, Kimmeldorf DJ, Koelling RA (1955) Conditioned taste aversion to saccharin resulting from exposure to gamma irradiation. Science 122:157–158

Gatley SJ, Meehan SM, Chen R, Pan D-F, Schechter MD, Dewey SL (1996) Place preference and microdialysis studies with two derivatives of methylphenidate. Life Sci 58:PL 345–PL 352

Gellert VF, Holtzman SG (1978) Development and maintenance of morphine tolerance and dependence in the rat by scheduled access to morphing drinking solutions. J Pharmacol Exp Ther 205:536–546

Ginsburg BC, Lamb RJ (2006) Fluvoxamine effects on concurrent ethanol- and food-maintained behaviors. Exp Clin Psychopharmacol 14:483–492

Glassman JM (1971) Agents with analgesic activity and dependence liability. In: Turner RA, Hebborn P (eds) Screening methods in pharmacology, vol II. Academic, New York/London, pp 227–248

Glennon RA, Young R (eds) (2011) Drug discrimination: applications to medicinal chemistry and drug studies. Wiley, New Jersey

Gmerek DE, Dykstra LA, Woods JH (1987) Kappa opioids in rhesus monkeys. III. Dependence associated with chronic administration. J Pharmacol Exp Ther 242:428–436

Goodwin AK, Griffiths RR, Brown PR, Froestl W, Jakobs C, Gibson KM, Weerts EM (2006) Chronic intragastric administration of gamma-butyrolactone produces physical dependence in baboons. Psychopharmacology 189:71–82

Hein DW, Young AM, Herling S, Woods JH (1981) Pharmacological analysis of the discriminative stimulus characteristics of ethylketazocine in the rhesus monkey. J Pharmacol Exp Ther 218:7–15

Henry PK, Howell LL (2009) Cocaine-induced reinstatement during limited and extended drug access conditions in rhesus monkeys. Psychopharmacology 204:523–529

Herling S, Woods JH (1981) Discriminative stimulus effects of narcotics: evidence for multiple receptor-mediated actions. Life Sci 28:1571–1584

Higgins GA, Joharchi N, Sellers EM (1993) Behavioral effects of the 5-hydroxytryptamine$_3$ receptor agonists 1-phenylbiguanide and m-chlorophenylbiguanide in rats. J Pharmacol Exp Ther 264:1440–1449

Hoffman DC (1998) The use of place conditioning in studying the neuropharmacology of drug reinforcement. Brain Res Bull 23:373–387

Hoffman DC, Donovan H (1995) Effects of typical, atypical, and novel antipsychotic drugs on amphetamine-induced place conditioning in rats. Drug Dev Res 36:193–198

Hoffmeister F (1979) Preclinical evaluation of reinforcing and aversive properties of analgesics. In: Beers RF, Bassett EG (eds) Mechanics of pain and analgesic compounds. Raven, New York, pp 447–466

Hoffmeister F (1988) A comparison of the stimulus effects of codeine in rhesus monkeys under the contingencies of a two lever discrimination task and a cross self-administration paradigm: tests of generalization to pentazocine, buprenorphine, tilidine, and different doses of codeine. Psychopharmacology 94:315–320

Holtz NA, Lozama A, Prisinzano TE, Carroll ME (2011) Reinstatement of methamphetamine seeking in male and female rats treated with modafinil and allopregnanolone. Drug Alcohol Depend (Epub ahead of print) PMID:21820819

Holtzman SG (1983) Discriminative stimulus properties of opioid agonists and antagonists. In: Cooper SJ (ed) Theory in psychopharmacology, vol 2. Academic, London, p 145

Holtzman SG (1990) Discriminative stimulus effects of drugs: relationship to potential for abuse. In: Adler MW, Cowan A (eds) Testing and evaluation of drugs of abuse, vol 6, Modern methods in pharmacology. Wiley-Liss, New York, pp 193–210

Hosenbocus S, Chahal R (2011) SSRIs and SNRIs: a review of the discontinuation syndrome in children and adolescents. J Can Acad Child Adolesc Psychiatry 20:60–67

Howell LL, Carroll FI, Votaw JR, Goodman MM, Kimmel HL (2007) Effects of combined dopamine and serotonin transported inhibitors on cocaine self-administration in rhesus monkeys. J Pharmacol Exp Ther 320:757–765

Iwamoto ET (1988) Dynorphin A (1–17) induces 'reward' in rats in the place conditioning paradigm. Life Sci 43:503–508

Jarbe TU, Swedberg MD (1998) Discriminative stimulus functions of CNS sedative drugs assessed by drug versus drug discrimination procedures in gerbils. Psychopharmacology 135:201–212

Kalant H, Khanna JM (1990) Methods for the study of tolerance. In: Adler MW, Cowan A (eds) Testing and evaluation of drugs of abuse, vol 6, Modern methods in pharmacology. Wiley-Liss, New York, pp 43–66

Katz JL (1986) Effects of clonidine and morphine on opioid withdrawal in rhesus monkeys. Psychopharmacology 88:392–397

Kennedy BC, Panksepp JB, Runckel PA, Lahvis GP (2011) Social influences on morphine-conditioned place preference in adolescent BALB/cJ and C57BL/6J mice. Psychopharmacology (Epub ahead of print) PMID:21837434

Kest B, Palmese CA, Hopkins E, Adler M, Juni A, Mogil JS (2002) Naloxone-precipitated withdrawal jumping in 11 inbred mouse strains: evidence for common genetic mechanisms in acute and chronic morphine physical dependence. Neuroscience 115:463–469

Khanna JM, Mayer JM, Lê AD, Kalant H (1984) Differential response to ethanol, pentobarbital and morphine in mice specially bred for ethanol sensitivity. Alcohol 1:447–451

Khroyan TV, Baker DA, Neisewander JL (1995) Dose-dependent effects of the D_3-preferring agonist 7-OH-DPAT on motor behaviors and place conditioning. Psychopharmacology 122:351–357

Khroyan TV, Fuchs RA, Baker DA, Neisewander JL (1997) Effects of D3-preferring agonists 7-OH-PIPAT and PD-128,907 on motor behaviors and place conditioning. Behav Pharmacol 8:65–74

Kitaichi K, Noda Y, Hasegawa T, Furukawa H, Nabeshima T (1996) Acute phencyclidine induces aversion, but repeated phencyclidine induces preference in the place conditioning test in rats. Eur J Pharmacol 318:7–9

Korkmaz S, Wahlström G (1999) Physical dependence after benzodiazepine treatments in rats: comparison of short and long treatments with diazepam and lorazepam. J Stud Alcohol 60:546–554

Kornetsky C, Bain B (1990) Brain-stimulation reward: a model for drug-induced euphoria. In: Adler MW, Cowan A (eds) Testing and evaluation of drugs of abuse, vol 6, Modern methods in pharmacology. Wiley-Liss, New York, pp 211–231

Kosten TA (1994) Clonidine attenuates conditioned aversion produced by naloxone-precipitated opiate withdrawal. Eur J Pharmacol 254:59–63

Lal H, Sherman GT (1980) Interceptive discriminative stimuli in the development of CNS drugs and a case of an animal model of anxiety. Annu Rep Med Chem 15:51–58

Langerman L, Zakowski MI, Piskoun B, Grant GJ (1995) Hot plate versus tail flick: evaluation of acute tolerance to continuous morphine infusion in the rat model. J Pharmacol Toxicol Methods 34:23–27

Lepore M, Vorel SR, Lowinson J, Gardner EL (1995) Conditioned place preference induced by Δ^9-tetrahydrocannabinol: comparison with cocaine, morphine, and food award. Life Sci 56:2073–2080

Littmann K, Heredia JM, Hoffmeister F (1979) Eine neue Methode zur enteralen Verabreichung von psychotrop wirksamen Substanzen beim Rhesusaffen. Arzneim Forsch/ Drug Res 29:1888–1890

Locke KW, Gorney B, Cornfeldt M, Fielding S (1991) Comparison of the stimulus effects of ethylketocyclazocine in Fischer and Sprague–Dawley rats. Drug Dev Res 23:65–73

Mamoon AM, Barnes AM, Ho IK, Hoskins B (1995) Comparative rewarding properties of morphine and butorphanol. Brain Res Bull 38:507–511

Marcus R, Kornetsky C (1974) Negative and positive intracranial thresholds: effects of morphine. Psychopharmacologia 38:1–13

Martellotta MC, Fattore L, Cossu G, Fratta W (1997) Rewarding properties of gamma-hydroxybutyric acid: an evaluation through place preference paradigm. Psychopharmacology 132:1–5

Martin WR, Eades CG, Thompson WO, Thompson JA, Flanary HG (1974) Morphine physical dependence in the dog. J Pharmacol Exp Ther 189:759–771

Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE (1976) The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther 197:517–532

Martin-Iverson MT, Reimer AR (1996) Classically conditioned motor effects do not occur with cocaine in an unbiased conditioned place preferences procedure. Behav Pharmacol 7:303–314

Martin-Iverson MT, Reimer AR, Sharma S (1997) Unbiased cocaine conditioned place preferences (CPP) obscures

conditioned locomotion, and nimodipine blockade of cocaine CPP is due to conditioned place aversions. Psychopharmacology 130:327–333
McMahon LR, Javors MA, France CP (2007) Changes in relative potency among positive GABA(A) receptor modulators upon discontinuation of chronic benzodiazepine treatment in rhesus monkeys. Psychopharmacology 192: 135–145
McMillan DE, Wessinger WD, Li M (2009) Effects of drugs and drug combination in pigeons trained to discriminate among pentobarbital, dizocilpine, a combination of these drugs, and saline. J Exp Anal Behav 92:387–412
Meert TF, Janssen PAJ (1989) Psychopharmacology of ritanserin: comparison with chlordiazepoxide. Drug Dev Res 18:119–144
Meert TF, de Haes P, Janssen PAJ (1989) Risperidone (R 64 766), a potent and complete LSD antagonist in drug discrimination by rats. Psychopharmacology 97:206–212
Meert TF, de Haes LAJ, Vermote PCM, Janssen PAJ (1990) Pharmacological validation of ritanserin and risperidone in the drug discrimination procedure in the rat. Drug Dev Res 19:353–373
Meisch RA, Carroll ME (1987) Oral drug self-administration: drugs as reinforcers. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 143–160
Morgan D, Roberts DC (2004) Sensitization to the reinforcing effects of cocaine following binge-abstinent self-administration. Neurosci Biobehav Rev 27:803–812
Mucha RF, Herz A (1985) Motivational properties of kappa and mu-opioid agonists studied with place and taste preference conditioning procedures. Psychopharmacology 82:241–245
Mucha RF, Iversen SD (1984) Reinforcing properties of morphine and naloxone revealed by conditioned place preferences: a procedural examination. Psychopharmacology 82:241–247
O'Dell LE, Chen SA, Smith RT, Specio SE, Balster RL, Paterson NE, Markou A, Zorilla EP, Koob GF (2007) Extended access to nicotine self-administration leads to dependence: circadian measures, withdrawal measures, and extinction behavior in rats. J Pharmacol Exp Ther 320:180–193
Olds J (1979) Drives and reinforcements: behavioral studies of hypothalamic functions. Raven, New York
Olds J, Killam KF, Bachy-Rita P (1956) Self-stimulation of the brain used as screening method for tranquilizing drugs. Science 124:265–266
Overton DA (1987) Applications and limitations of the drug discrimination method for the study of drug abuse. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 291–340
Pain L, Oberling P, Sandner G, Di Scala G (1997) Effect of midazolam on propofol-induced positive affective state assessed by place conditioning in rats. Anesthesiology 87:935–943
Papp M, Moryl E, Maccechini ML (1996) Differential effects of agents acting at various sites of the NMDA receptor complex in a place preference conditioning model. Eur J Pharmacol 317:191–196
Parker LA (1996) LSD produces place preference and flavor avoidance but does not produce flavor aversion in rats. Behav Neurosci 110:503–508
Paxinos G, Watson C (1982) The rat in stereotaxic coordinates. Academic, Sidney
Perks SM, Clifton PG (1997) Reinforcer revaluation and conditioned place preference. Physiol Behav 61:1–5
Pierce TL, Raper C (1995) The effects of laboratory handling procedures on naloxone-precipitated withdrawal behavior in morphine-dependent rats. J Pharmacol Toxicol Methods 34:149–155
Pierce TL, Hope W, Raper C (1996) The induction and quantitation of methadone dependence in the rat. J Pharmacol Toxicol Methods 36:137–146
Porsolt RD, Castagné V, Dürmüller N, Lemaire M, Moser P, Roux S, France Central nervous system (CNS) safety pharmacology studies
Riba P, Ben Y, Smith AP, Furst S, Lee NM (2002) Morphine tolerance in spinal cord is due to interaction between mu- and delta-receptors. J Pharmacol Exp Ther 300:265–272
Rodríguez R, Luján M, Campos AE, Chorné R (1978) Morphine-dependence in the isolated guinea pig ileum and its modification by p-chlorophenylalanine. Life Sci 23: 913–920
Rothwell PI, Thomas MJ, Gewirtz JC (2011) Protracted manifestations of acute dependence after a single morphine exposure. Psychopharmacology (Epub ahead of print) PMID:21833504
Saelens JK, Granat FR, Sawyer WK (1971) The mouse jumping test: a simple screening method to estimate the physical dependence capacity of analgesics. Arch Int Pharmacodyn Ther 190:213–218
Sante AB, Nobre MJ, Brandao ML (2000) Place aversion induced by blockade of mu or activation of kappa opioid receptors in the dorsal periaqueductal gray matter. Behav Pharmacol 11:583–589
Sañudo-Peña CM, Tsou K, Delay ER, Hohman AG, Force M, Walker JM (1997) Endogenous cannabinoids as an aversive or counter-rewarding system in the rat. Neurosci Lett 223:125–128
Schechter MD, Meehan SM (1994) Conditioned place aversion produced by dopamine release inhibition. Eur J Pharmacol 260:133–137
Schwandt ML, Higley JD, Suomi SJ, Heilig M, Barr CS (2008) Rapid tolerance and locomotor sensitization in ethanol-naïve adolescent rhesus macaques. Alcohol Clin Exp Res 32:1217–1228
Seevers MH (1936) Opiate addiction in the monkey. I. Methods of study. J Pharmacol Exp Ther 56:147–156
Seevers MH, Deneau GA (1963) Physiological aspects of tolerance and dependence. In: Root WS, Hoffman FG (eds) Physiological Pharmacology, vol I. Academic, New York/London, p 565
Self DW, Stein L (1992) Receptor subtypes in opioid and stimulation reward. Pharmacol Toxicol 70:87–94
Sevak RJ, Owens WA, Koek W, Galli A, Daws LC, France CP (2007) Evidence for D2 receptor mediation of amphetamine-induced normalization of locomotion and dopamine transporter function in hypoinsulinemic rats. J Neurochem 101:151–159

Sevak RJ, Koek W, Daws LC, Owens WA, Galli A, France CP (2008a) Behavioral effects of amphetamine in streptozotocin-treated rats. Eur J Pharmacol 581:105–112

Sevak RJ, Koek W, Owens WA, Galli A, Daws LC, France CP (2008b) Feeding conditions differentially affect the neurochemical and behavioral effects of dopaminergic drugs in male rats. Eur J Pharmacol 592:109–115

Shannon HE, Holtzman SG (1976) Evaluation of the discriminative effects of morphine in the rat. J Pharmacol Exp Ther 198:64–65

Shannon HE, Holtzman SG (1986) Blockade of the discriminative effects of morphine by naltrexone and naloxone. Psychopharmacologia 50:119–124

Shelton KL, Dukat M, Allan AM (2004) Effects of 5-HT_3 receptor over-expression on the discriminative stimulus effects of ethanol. Alcohol Clin Exp Res 28:1161–1171

Sherman G, Lal H (1979) Discriminative stimulus properties of pentylenetetrazol and begrimide: some generalization and antagonism tests. Psychopharmacology 64:315–319

Sherman GT, Lal H (1980) Generalization and antagonism studies with convulsant, GABAergic and anticonvulsant drugs in rats trained to discriminate pentylenetetrazol from saline. Neuropharmacology 19:473–479

Sherman GT, Miksic S, Lal H (1979) Lack of tolerance development to benzodiazepines in antagonism of the pentylenetetrazol discriminative stimulus. Pharmacol Biochem Behav 10:795–797

Shippenberg TS, Herz A (1987) Place preference conditioning reveals the involvement of D_1-dopamine receptors in the motivational properties of mu and kappa opioid agonists. Brain Res 436:169–172

Shippenberg TS, Bals-Kubik R, Herz A (1987) Motivational properties of opioids: evidence that an activation of δ-receptors mediate reinforcement processes. Brain Res 436:234–239

Smith FL, Javed RR, Elzey MJ, Dewey WL (2003) The expression of a high level of morphine antinociceptive tolerance in mice involves both PKC and PKA. Brain Res 985:78–88

Steinpreis RE, Kramer MA, Mix KS, Piwowarczyk MC (1995) The effects of MK801 on place conditioning. Neurosci Res 22:427–430

Steinpreis RE, Rutell AL, Parrett FA (1996) Methadone produces conditioned place preference in the rat. Pharmacol Biochem Behav 54:339–431

Stewart JL, McMahon LR (2010) Rimonabant-induced delta9-tetrahydrocannabinol withdrawal in rhesus monkeys: discriminative stimulus effects and other withdrawal signs. J Pharmacol Exp Ther 334:347–356

Stolerman IP, Mariathasan EA, White JA, Olufsen KS (1999) Drug mixtures and ethanol as compound internal stimuli. Pharmacol Biochem Behav 64:221–228

Stolerman IP, Chamberlain S, Bizarro L, Fernandes C, Schalkwyk L (2004) The role of nicotinic receptor alpha 7 subunits in nicotine discrimination. Neuropharmacology 46:363–371

Sufka KJ (1994) Conditioned place preference paradigm: a novel approach for analgesic drug assessment against chronic pain. Pain 58:355–366

Suzuki T, Misawa M (1995) Sertindole antagonizes morphine-, cocaine-, and methamphetamine-induced place preference in the rat. Life Sci 57:1277–1284

Suzuki T, Funada M, Narita M, Misawa M, Nagase H (1991) Pertussis toxin abolishes μ and δ opioid agonist-induced place preference. Eur J Pharmacol 205:85–88

Suzuki T, Funada M, Narita M, Misawa M, Nagase H (1993) Morphine-induced place preference in the CXBK mouse: characteristics of μ opioid receptor subtypes. Brain Res 602:45–52

Tsuji M, Nakagawa Y, Ishibashi Y, Yoshii T, Takashima T, Shimada M, Suzuki T (1996) Activation of ventral tegmental $GABA_B$ receptors inhibits morphine-induced place preference in rats. Eur J Pharmacol 313:169–173

Turenne SD, Miles C, Parker LA, Siegel S (1996) Individual differences in reactivity to the rewarding/aversive properties of drugs: assessment by taste and place conditioning. Pharmacol Biochem Behav 53:511–516

Tzschenke M (1998) Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. Prog Neurobiol 56:613–6672

Van der Kooy D (1987) Place conditioning: a simple and effective method for assessing the motivational properties of drugs. In: Bozarth MA (ed) Methods of assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 229–240

van Heest A, Hijzen TH, Slangen JL, Oliver B (1992) Assessment of the stimulus properties of anxiolytic drugs by means of the conditioned taste aversion procedure. Pharmacol Biochem Behav 42:487–495

Villarreal JE, Martinez JN, Castro A (1977) Validation of a new procedure to study narcotic dependence in the isolated guinea pig ileum. Bull Problems of Drug Dependence, pp 305–314

VonVoigtlander PF, Lewis RA (1983) A withdrawal hyperalgesia test for physical dependence: evaluation of μ and mixed-partial opioid agonists. J Pharmacol Methods 10:277–282

Voorhees CM, Cunningham CL (2001) Involvement of the orexin/hypocretin system in ethanol conditioned place preference. Psychopharmacology 214:805–818

Wang Z, Woolverton WL (2007) Estimating the relative reinforcing strength of (+/−)-3,4-methylenedioxymethamphetamine (MDMA) and its isomers in rhesus monkeys: comparison to (+)-methamphetamine. Psychopharmacology 189:483–488

Wang JH, Wu XJ, Li CY, Wei JK, Jiang JJ, Liu CR, Yu CY, Carlson S, Hu XT, Ma H, Duan W, Ma YY (2011) Effect of morphine on conditioned place preference in rhesus monkeys. Addict Biol (Epub ahead or print) PMID:21305991

Way EL (1993) Opioid tolerance and physical dependence and their relationship. In: Herz A, Akil H, Simon EJ (eds) Opioids II, vol 104, Handbook of experimental pharmacology. Springer, Berlin/Heidelberg/New York, pp 573–596, chapter 53

Way EL, Loh HH, Shen FH (1969) Simultaneous quantitative assessment of morphine tolerance and physical dependence. J Pharmacol Exp Ther 167:1–8

Weeks JR, Collins RJ (1987) Screening for drug reinforcement using intravenous self-administration in the rat. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 35–43

Weerts EM, Goodwin AK, Griffiths RR, Brown PR, Froestl W, Jakobs C, Gibson KM (2005) Spontaneous and precipitated withdrawal after chronic intragastric administration of gamma-hydroxybutyrate (GHB) in baboons. Psychopharmacology 179:678–687

Winsauer PJ, Silvester KR, Moerschbaecher JM, France CP (2000) Cocaine self-administration in monkeys: effects on the acquisition and performance of response sequences. Drug Alcohol Depend 59:51–61

Woods JH, France CP, Winger G, Bertamio AJ, Schwarz-Stevens K (1993) Opioid abuse liability assessment in rhesus monkeys. In: Herz A, Akil H, Simon EJ (eds) Opioids II, vol 104, Handbook of experimental pharmacology. Springer, Berlin/Heidelberg/New York, pp 609–632, chapter 55

Woolverton WL, Nader MA (1990) Experimental evaluation of the reinforcing effects of drugs. In: Adler MW, Cowan A (eds) Testing and evaluation of drugs of abuse, vol 6, Modern methods in pharmacology. Wiley-Liss, New York, pp 165–192

Woolverton WL, Schuster CL (1983) Intragastric self-administration in rhesus monkeys under limited access conditions: methodological studies. J Pharmacol Methods 10:93–106

Yokel RA (1987) Intravenous self-administration: response rates, the effects of pharmacological challenges, and drug preference. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, New York/Berlin/Heidelberg, pp 1–33

Yoshimura K, Horiuchi M, Konishi M, Yamamoto KI (1993) Physical dependence on morphine induced in dogs via the use of miniosmotic pumps. J Pharmacol Toxicol Methods 30:85–95

Zarrindast MR, Meshkani J, Rezayof A, Rotami P (2010) Nicotinic acetylcholine receptors of the dorsal hippocampus and the basolateral amygdala are involved in ethanol-induced conditioned place preference. Neuroscience 168:505–513