*Brain Research Bulletin*, Vol. 23, pp. 373–387. © Pergamon Press plc, 1989. Printed in the U.S.A.

0361-9230/89 $3.00 + .00

MEETING REPORT

# The Use of Place Conditioning in Studying the Neuropharmacology of Drug Reinforcement

DIANE C. HOFFMAN

*Center for Studies in Behavioral Neurobiology, Department of Psychology*
*Concordia University, 1455 de Maisonneuve Boulevard W., Montreal, Quebec H3G 1M8*

HOFFMAN, D. C. *The use of place conditioning in studying the neuropharmacology of drug reinforcement.* BRAIN RES BULL **23**(4/5) 373–387, 1989.—The place conditioning paradigm has proven successful in identifying the neural mechanisms of drug reinforcement. Two classes of drugs, opiates and psychomotor stimulants, have received the most study, and in each case an important role for DA neurons of the mesolimbic system has been established. Moreover, both receptor subtypes, D1 and D2, appear to be involved. Despite this progress, the substrates of drug reward are not completely understood. First, a role for DA has not been established for all stimulants: DA receptor blockade failed to affect conditioned place preferences produced by the stimulants methylphenidate, nomifensine, or bupropion. Second, preliminary evidence suggests that intact serotonergic transmission is important in morphine place conditioning, but a similar consistent finding has not been observed with amphetamine place conditioning. Further study may reveal an interesting dissociation of serotonin's role in the rewarding effects of psychomotor stimulants and opiates. Finally, the role of the opiate receptor subtype kappa is not known; also, the significance of the several anatomical sites that support opiate place conditioning remains unclear.

Dopamine D1 and D2 receptors Noradrenaline Opiates Opiate receptor subtypes Place conditioning Psychomotor stimulants Reinforcement Serotonin

THE behavioral effects of rewarding stimuli can be separated into three broad categories. First, stimuli are classified as rewarding or punishing on the basis of their ability to evoke approach or withdrawal, respectively (91). Second, when delivery of a reward is contingent upon a particular response, it increases the probability that the response will reappear in a similar situation. Skinner (99) labelled this effect *operant* reinforcement. Rewarding stimuli have a third behavioral effect described by Pavlov (80): when rewarding stimuli are paired with neutral environmental stimuli, the initially neutral stimuli gain the capacity of eliciting the unconditioned behavioral effects initially associated only with the unconditioned reward. Skinner defined this as *respondent* reinforcement and argued that it was different in principle than operant reinforcement. In each case, rewarding stimuli alter behavior in a predictable manner, with the change in behavior defined as learning. Learning theorists disagree, however, as to the mechanisms underlying these behavioral changes.

Neuroscientists have been interested in identifying the neural mechanisms that underly the behavioral effects of reward. Results from a large number of studies suggest an important role for the neurotransmitter dopamine (DA) [cf. (16, 118, 120)]. For example, it has been shown that well-established behavior that is under the control of a reinforcing stimulus (e.g., lever-pressing for food) is disrupted in animals treated with DA receptor antagonists [cf. (118)].

DA receptor blockers also produce some degree of motor debilitation; for example, these drugs (as well as selective lesions of central DA pathways) suppress locomotor activity (112) and induce catalepsy (87). This creates a problem when interpreting the effects of DA antagonists on behavior that is controlled or influenced by rewarding stimuli: it is often difficult to establish if the disruption (in food-rewarded lever-pressing) results from a nonspecific effect of the drug—on motor capacity or sensory-motor integration—or an effect of the drug on reward mechanisms. This difficulty with interpretation has prompted sophisticated approaches to studying the role of DA in reward.

## THE PRINCIPLE OF CONDITIONED REINFORCEMENT

It is clear that challenging the DA system impairs reward function, and it is equally clear that it *also* causes some degree of debilitation. It would be useful to have a paradigm in which the behavioral measure of reward is *not* contaminated or influenced by nonspecific debilitating effects of DA receptor blockers. Behavioral paradigms based on the principle of conditioned reinforce-

ment have this advantage (17,31).

As described above, rewarding stimuli have the important capability of establishing neutral environmental stimuli as conditioned rewards (i.e., Pavlovian or respondent conditioning). That is, when a rewarding stimulus is repeatedly paired with a neutral stimulus, this stimulus, by virtue of the Pavlovian conditioning, acquires rewarding properties. The environmental stimulus, referred to as a conditioned or "secondary" reinforcer, is now capable of *eliciting* approach (the first behavioral effect of rewards described above). Alternatively, the conditioned reinforcer can serve as an effective stimulus for the acquisition of an operant response (e.g., lever-pressing) (the second behavioral effect of rewards). In both cases, the effects of reinforcing stimuli are observable and predictable changes in behavior occur; however, the mechanisms which underlie the behavioral changes—whether it is stimuli and responses or stimuli and other stimuli that are being associated—are still debated amongst learning theorists.

The role of DA in the establishment of conditioned reinforcement can be examined by using a conditioned reinforcement paradigm. The advantage of this technique is that DA antagonists are administered only during the conditioning phase of the experiment (e.g., tone-food pairings) when response demands are minimal. The evidence of conditioning or lack of conditioning is obtained from subsequent testing sessions when the animal is drug-free and thus unaffected by any performance-limiting consequences of DA blockers. Thus, the confounds associated with drug-induced motor impairments are minimized because the dependent variable is measured in an animal that is *drug-free*.

For example, Hoffman and Beninger (44) gave food-deprived animals pairings of a light with food pellets. The conditioned reinforcing effectiveness of the light was later determined in a test session by exposing animals to a chamber outfitted with two levers, one of which when pressed resulted in a brief presentation of the stimulus previously paired with reward. Control rats showed an elevation of response rates on the reward-related lever which was interpreted as evidence for conditioned *operant* reinforcement. In contrast, animals pretreated with pimozide during the light-food pairings, did not show an increase in responding for the light in the drug-free test despite the fact that the rats ate the food pellets during conditioning (44). This suggested an important role for DA in the acquisition of conditioned reinforcement.

Place conditioning may be viewed as an alternative method for establishing conditioned reinforcement. In this case, a food-deprived animal is exposed to a box which consists of two compartments (which differ in floor texture and wall color) often joined by a small tunnel. Food delivery is paired with confinement to one compartment and not the other. Later, in the absence of the rewarding stimulus, the animal demonstrates a relative increase in the amount of time spent in the environment previously associated with food compared to a neutral environment. This shift in preference is attributed to the conditioned rewarding properties of the environmental stimuli which now *elicit* an approach response.

Place conditioning has been demonstrated with rewarding stimuli such as food (79, 101, 111), sucrose solutions (117) or lateral hypothalamic brain stimulation (35). Furthermore, when rats were treated with selective DA receptor antagonists during the pairings, the establishment of place conditioning was disrupted (35,101). There has been one exception to this finding: Tombaugh *et al.* (111) failed to block food-induced place preference in rats treated with pimozide. The animals in this study, unlike those of Spyraki *et al.* (101), were food-deprived during the test and this may explain (in some unknown manner) the inconsistent results. The importance of this variable was illustrated by Bechara and van der Kooy (14) who discovered that ibotenic acid lesions of the pedunculopontine nucleus abolished food-induced place preferences only when the rats were sated during the test.

## USE OF THE PLACE CONDITIONING PARADIGM IN ASSESSING THE REWARDING PROPERTIES OF DRUGS

Drugs abused by humans are often used to study the neuropharmacology of reward. These drugs are self-administered by animals and are effective unconditioned stimuli for establishing conditioned operant reinforcement. For example, when intravenous injections of the DA agonists apomorphine or piribedil were repeatedly paired with a buzzer, drug-free animals subsequently showed elevated responding on a lever that when pressed resulted in a brief presentation of the buzzer (31). Unfortunately, the conditioned operant reinforcement paradigm has been used by only one group of investigators; thus, most evidence of drug reward involving conditioned reinforcement comes from the place conditioning paradigm.

As predicted, self-administered drugs are effective in producing conditioned place preferences. That is, after receiving pairings of a drug with a particular environment, an animal that is now drug-free spends more time in this environment than in a neutral environment. The increase in time is attributed to the conditioned reinforcing properties of the environmental stimuli which are now capable of attracting the animal.

The mechanism by which environmental stimuli acquire the ability to elicit an approach response is not completely understood (119). Unlike the case with conventional reinforcing stimuli (e.g., food or water), a strict Pavlovian analysis of drug-induced place conditioning is inadequate. Because drugs acquire access to the central nervous system without passing through any sensory systems, there can be no unconditioned response of approach, and thus, there is no *unconditioned response* which corresponds to the *conditioned response* of approaching the environmental stimuli. One can only speculate at this point: perhaps drugs that produce place preferences directly activate neural mechanisms mediating approach responses and these responses become associated with the environmental stimuli.

Despite our incomplete understanding of the learning principles that explain place conditioning, the procedure is useful for demonstrating the rewarding properties of drugs and there are several advantages for using this paradigm. First, as previously mentioned, the reinforcing effects of a drug are measured in an animal that is drug-free. Thus, any changes in unconditioned motor activity do not directly influence measurement of the dependent variable (time spent in the drug-paired environment). Second, the short-term nature of the experiments (lasting on average between 1 to 3 weeks) and the sensitivity of the paradigm for demonstrating place conditioning (preference or aversion) in as little as one drug pairing (7, 51, 74) provide other obvious advantages.

Two general approaches are used when studying the neural mechanisms of drug reward. First, drugs with known pharmacological properties (e.g., selective for a receptor subtype) are tested in the place conditioning paradigm to determine their reinforcing potential; additional information regarding the anatomical substrate can be obtained by administering the drugs into discrete brain nuclei. Second, the effects of selective receptor antagonists or lesions on the establishment of drug-induced place conditioning are evaluated. With each approach, inferences concerning the role of neurotransmitters, receptor subtypes and anatomical substrates are made.

Two classes of drugs, psychomotor stimulants and opiates, have received the most study and the data gathered on each are reviewed below. Table 1 summarizes the effects of a large number of drugs that have been tested in the place conditioning paradigm;

TABLE 1

DRUGS AND THEIR EFFECTS IN THE PLACE CONDITIONING PARADIGM

| Drug | Dose/Route* | Effect | Reference |
|---|---|---|---|
| | Psychomotor Stimulants (Dopamine Agonists) | | |
| A. Mixed Agonists | | | |
| (+)-Amphetamine | Systemic | Preference | (4, 23–25, 28, 30, 33, 37, 43, 45, 46, 56, 59, 60, 62, 67, 77, 81, 85, 90, 95, 102, 106, 110) |
| | Nuc. Accumbens | Preference | (5, 26, 27) |
| | Amygdala | No effect | (27) |
| | Caudate | No effect | (26,27) |
| | mPFC | No effect | (27) |
| | Area Postrema | No effect | (27) |
| (−)-Amphetamine | Systemic | Preference | (37) |
| Apomorphine | Systemic | Preference | (79, 102, 109, 114) |
| | High dose | Aversion | (18) |
| Bupropion | Systemic | Preference | (78) |
| Cocaine | Systemic | Preference | (9, 48, 62, 66, 68, 74, 76, 90, 103, 105, 107) |
| | ICV | Preference | (68) |
| | Nuc. Accumbens | Preference | (5) |
| Methylphenidate | Systemic | Preference | (28, 65, 67) |
| Nomifensine | Systemic | Preference | (65) |
| B. Preferential D1 Receptor Agonists | | | |
| SKF 38393 | Systemic | No effect | (38) |
| | Systemic | Aversion | (45,46) |
| SKF 82526 | Systemic | No effect | (45) |
| C. Preferential D2 Receptor Agonists | | | |
| Bromocriptine | Systemic | Preference | (47) |
| | ICV | Preference | (68) |
| Quinpirole | Systemic | Preference | (45–47) |
| N-0437 | Systemic | Preference | (38) |
| | Dopamine Antagonists | | |
| A. Mixed Antagonists | | | |
| Alpha-Flupenthixol | Systemic | No effect | (62) |
| (l)-Butaclamol | Systemic | No effect | (50) |
| (d)-Butaclamol | Systemic | No effect | (50) |
| Haloperidol | Systemic | No effect | (65, 93, 100, 101, 104) |
| Pimozide | Systemic | No effect | (22) |
| B. Preferential D1 Receptor Antagonists | | | |
| SCH 23390 | Systemic | No effect | (46) |
| | Systemic | Aversion | (97,98) |
| C. Preferential D2 Receptor Antagonists | | | |
| Domperidone | Systemic | No effect | (100) |
| Metoclopramide | Systemic | Preference | (46) |
| Spiroperidol | Systemic | No effect | (50,98) |
| Sulpiride | Systemic | No effect | (38,98) |

TABLE 1
CONTINUED

| Drug | Dose/Route* | Effect | Reference |
|---|---|---|---|
| | | Opiate Agonists | |
| A. Mixed Agonists | | | |
| Beta-Endorphin | ICV | Preference | (2) |
| [D-Ala$^2$]-Leu-Enkephalinamide | ICV | Preference | (53) |
| [D-Ala$^2$]-Met$^5$-Enkephalinamide | VTA | Preference | (83,84) |
| [D-Ala$^2$]-Methionine Enkephalin | ICV | Preference | (108) |
| Dextrorphan | Systemic | No effect | (71,74) |
| Dynorphin A [1–17] | ICV | Preference | (51) |
| Dynorphin A [2–17] | ICV | No effect | (51) |
| Etorphine | Systemic | Preference | (71,74) |
| Heroin | Systemic | Preference | (2, 21, 22, 34, 58, 88, 89, 104) |
| Levorphanol | Systemic | Preference | (71,74) |
| Leu-enkephalin | Systemic | Preference | (42) |
| | Systemic | Aversion | (42) |
| | ICV | No effect | (51) |
| Morphine | Systemic | Preference | (1, 6–8, 10–12, 14, 15, 19, 23, 34, 49, 53, 55–57, 59, 62, 63, 70–74, 77, 86, 93, 94, 96–98, 106, 108, 115, 116, 121) |
| | 0.05 mg/kg IP | Aversion | (12, 15, 121) |
| | Intrathecal | Preference | (1) |
| | ICV | Preference | (96,113) |
| | Hippocampus | Preference | (29) |
| | Nuc. Accumbens | Preference | (113) |
| | LH | Preference | (113) |
| | PAG | Preference | (113) |
| | VTA | Preference | (20,82) |
| | Amygdala | No effect | (113) |
| | Caudate | No effect | (113) |
| | Nuc. Ambiguous | No effect | (113) |
| (+)-Morphine | Systemic | No effect | (71) |
| (−)-Morphine | Systemic | Preference | (71) |
| Thiorphan | VTA | Preference | (39) |
| B. Preferential Mu Receptor Agonists | | | |
| Fentanyl | Systemic | Preference | (36,70) |
| Sufentanyl | Systemic | Preference | (70) |
| C. Preferential Delta Receptor Agonists | | | |
| [D-Pen$^2$,D-Pen$^5$]-Enkephalin | ICV | Preference | (96) |
| D. Preferential Kappa Receptor Agonists | | | |
| Bremazocine | Systemic | Aversion | (49) |
| (+)-Bremazocine | Systemic | No effect | (70) |
| (−)-Bremazocine | Systemic | Aversion | (70) |
| Ethylketocyclazocine | Systemic | Preference | (49) |
| | Systemic | No effect | (70) |
| Ketocyclazocine | Systemic | Preference | (49) |
| MR 2034 | Systemic | No effect | (70) |
| Trifluadom | Systemic | No effect | (70) |
| U50,488 | Systemic | Aversion | (13, 49, 70, 73) |
| U69,593 | Systemic | Aversion | (97,98) |

TABLE 1
CONTINUED

| Drug | Dose/Route* | Effect | Reference |
|---|---|---|---|
| | | Opiate Antagonists | |
| A. Mixed Antagonists | | | |
| Methylnaloxone | Systemic | No effect | (40) |
| | ICV | Aversion | (40) |
| Methylnaloxonium | Systemic | No effect | (42) |
| Methylnaltrexone | Systemic | Preference | (12) |
| | ICV | No effect | (69) |
| Naltrexone | Systemic | Aversion | (12) |
| | | No effect | (69) |
| Naloxone | Systemic | No effect | (7, 22, 83,94) |
| | Systemic | Aversion | (2, 15, 34, 49, 70, 73, 75, 98, 105) |
| | VTA | No effect | (39) |
| | 0.1 mg/kg IP | Preference | (12) |
| (−)-Naloxone | Systemic | Aversion | (74) |
| (+)-Naloxone | Systemic | No effect | (74) |
| B. Preferential Delta Receptor Antagonists | | | |
| ICI 174,864 | ICV | No effect | (96) |
| C. Preferential Kappa Receptor Antagonists | | | |
| Mr 2266 | Low doses | Preference | (13) |
| | High doses | Aversion | (13) |
| l-Mr 2266BS | Systemic | Aversion | (49) |
| Mr 2267 | Systemic | No effect | (13) |
| | Very high dose | Preference | (13) |
| l-WIN 44,441-3 | Systemic | Preference | (49) |

*In some cases, where a differential effect was observed, the dose is given. When the drug was administered centrally into a discrete brain region, the region is listed.

Abbreviations: ICV: intracerebroventricular; IP: intraperitoneal; LH: lateral hypothalamus; PAG: periaqueductal gray; VTA: ventral tegmental area.

Table 2 summarizes the effects of selective receptor antagonists or lesions on the establishment of place conditioning produced by drugs shown in Table 1.

## PSYCHOMOTOR STIMULANTS

### *The Effects of Stimulants and DA Receptor Antagonists in the Place Conditioning Paradigm*

*Systemic administration.* The psychomotor stimulants (+)-amphetamine, cocaine, bupropion, methylphenidate, nomifensine, and apomorphine have been shown to produce conditioned place preferences (Table 1). A conditioned place *aversion* with apomorphine was also reported, however, a very high dose (15 mg/kg) was used.

These drugs share the common property of facilitating dopaminergic transmission either by stimulating the release of DA, inhibiting DA uptake or directly stimulating DA receptors. Because two subpopulations of DA receptors exist (54), the effects of DA receptor agonists which preferentially bind to either the D1 or D2 receptor were tested in the place conditioning paradigm.

Whereas the D2 agonists bromocriptine, N-0437, and quinpirole produced significant place preferences (38, 45–47), the D1 agonist SKF 38393 resulted in a significant and dose-dependent place aversion (45). The aversion was probably not mediated peripherally because a similar test with the D1 agonist SKF 82526, which does not readily pass through the blood-brain barrier, was not effective in producing an aversion (although only one dose was tested) (45).

Drugs which block DA receptors have also been tested in the place conditioning paradigm (Table 1). No significant effects have been reported with *mixed* DA receptor antagonists. Some studies reported that the selective D1 receptor antagonist SCH 23390 induced a conditioned place aversion (97,98), although another reported no effect (46). The time delay between SCH 23390 administration and placement in the conditioning apparatus differed in these studies (no delay vs. 1 hr) and may account for the discrepancy. Interestingly, a place preference was observed in rats treated with the D2 receptor antagonist metoclopramide (46); however, a similar effect was not observed with other D2 antagonists such as sulpiride or spiroperidol (38, 50, 98).

*Effects of centrally administered psychomotor stimulants.* It appears that DA terminals of the nucleus accumbens (which originate in the ventral tegmental area) mediate the reinforcing

TABLE 2

EFFECTS OF ANTAGONISTS OR LESIONS ON PLACE CONDITIONING PRODUCED BY PSYCHOMOTOR STIMULANTS (I) OR OPIATES (II)

| Pretreatment | Effect | Reference |
|---|---|---|
| **I. Psychomotor Stimulants** | | |
| A. Systemic Amphetamine Conditioned Place Preference (CPP) | | |
| Mixed DA Receptor Antagonists | | |
| Alpha-flupenthixol | Antagonism | (62) |
| Haloperidol | Antagonism | (67,102) |
| Clozapine | No effect | (24) |
| D1 Receptor Antagonist | | |
| SCH 23390 | No effect | (38) |
| | Antagonism | (46,59) |
| D2 Receptor Antagonists | | |
| Metoclopramide | Antagonism | (46) |
| | No effect | (24) |
| Sulpiride | Antagonism | (24) |
| | Potentiation | (38) |
| 5-HT Uptake Inhibitor | | |
| Zimelidine | Antagonism | (56) |
| 5-$HT_2$ Receptor Antagonist | | |
| Ritanserin | Antagonism | (77) |
| 5-$HT_3$ Receptor Antagonists | | |
| ICS 205-930 | No effect | (23) |
| MDL 72222 | No effect | (23) |
| Lesions | | |
| Intra-accumbens 5,7-DHT | No effect | (106) |
| Intra-accumbens 6-OHDA | Antagonism | (102) |
| Peripheral NA Depletion | No effect | (102) |
| Other Pretreatments | | |
| Progabide (GABA mimetic) | No effect | (33) |
| Intra-VTA Cholecystokinin | Potentiation | (81) |
| B. Intra-Accumbens Amphetamine | | |
| DA Receptor Antagonists | | |
| Intra-accumbens cis-flupenthixol | Antagonism | (5) |
| Intra-accumbens trans-flupenthixol | No effect | (5) |
| C. Systemic (IP or SC) Cocaine CPP | | |
| Mixed DA Receptor Antagonists | | |
| Alpha-flupenthixol | No effect | (62) |
| Haloperidol | No effect | (103) |
| Pimozide | No effect | (68,103) |
| Lesions: | | |
| Intra-accumbens 6-OHDA | No effect | (103) |
| mPFC lesions | Antagonism | (48) |
| Peripheral NA Depletion | No effect | (103) |
| Central NA Depletion | No effect | (103) |
| D. IV or ICV Cocaine CPP | | |
| Mixed DA Receptor Antagonists | | |
| Pimozide | Antagonism | (68) |
| Haloperidol | Antagonism | (107) |
| E. Intra-accumbens Cocaine CPP | | |
| DA Receptor Antagonists | | |
| Intra-accumbens cis-flupenthixol | Antagonism | (5) |
| Intra-accumbens trans-flupenthixol | No effect | (5) |

TABLE 2

CONTINUED

| Pretreatment | Effect | Reference |
|---|---|---|
| F. Systemic Apomorphine CPP | | |
| Lesions | | |
| Intra-accumbens 6-OHDA | Potentiation | (109,114) |
| G. Systemic Bupropion CPP | | |
| DA Receptor Antagonists | | |
| Haloperidol | No effect | (78) |
| Sulpiride (D2 antagonist) | No effect | (78) |
| H. Systemic Methylphenidate CPP | | |
| DA Receptor Antagonist | | |
| Haloperidol | No effect | (65,67) |
| Lesion | | |
| ICV 6-OHDA | No effect | (65) |
| I. Systemic Nomifensine CPP | | |
| DA Receptor Antagonist | | |
| Haloperidol | No effect | (65) |
| J. Systemic Quinpirole CPP | | |
| D1 Receptor Antagonist | | |
| SCH 23390 medium dose | Antagonism | (46) |
| high dose | No effect | (46) |
| D2 Receptor Antagonist | | |
| Metoclopramide medium dose | Antagonism | (46) |
| high dose | No effect | (46) |
| K. Systemic SKF 38393 Conditioned Place Aversion (CPA) | | |
| D1 Receptor Antagonist | | |
| SCH 23390 | Antagonism | (46) |
| D2 Receptor Antagonist | | |
| Metoclopramide | Antagonism | (46) |
| **II. Opiates** | | |
| A. Systemic Morphine CPP | | |
| Opiate Receptor Antagonist | | |
| Naloxone | Antagonism | (7, 49, 74, 94) |
| Mixed DA Receptor Antagonists | | |
| Alpha-Flupenthixol | No effect | (62) |
| Haloperidol | No effect | (62) |
| | Antagonism | (93) |
| D1 Receptor Antagonist | | |
| SCH 23390 | Antagonism | (59, 97, 98) |
| D2 Receptor Antagonists | | |
| Spiroperidol | No effect | (98) |
| Sulpiride | No effect | (98) |
| 5-HT Uptake Inhibitor | | |
| Zimelidine | No effect | (56) |
| 5-$HT_2$ Receptor Antagonist | | |
| Ritanserin | Antagonism | (77) |
| 5-$HT_3$ Receptor Antagonists | | |
| ICS 205-930 | Antagonism | (23) |
| MDL 72222 | Antagonism | (23) |
| 5-HT Synthesis Inhibitor | | |
| p-Chlorophenylalanine | No effect | (93) |
| Catecholamine Synthesis Inhibitor | | |
| AMPT | Antagonism | (93) |

TABLE 2
CONTINUED

| Pretreatment | Effect | Reference |
|---|---|---|
| NA Synthesis Inhibitor | | |
| DETC | No effect | (93) |
| Lesions | | |
| Intra-accumbens 5,7-DHT | Antagonism | (106) |
| Nucleus Accumbens | Antagonism | (55) |
| Central Catecholamine Depletion (6-OHDA) | Antagonism | (93) |
| Visceral Cortex (6-OHDA) | No effect | (121) |
| Pedunculopontine Nucleus | Antagonism | (14) |
| Arcuate Hypothalamus | No effect | (73) |
| Neonatal Capsaicin | No effect | (15) |
| Vagotomy | No effect | (12) |
| B. ICV Morphine CPP | | |
| Delta Receptor Antagonist | | |
| ICI 174,864 (ICV) | No effect | (96) |
| C. Intra-VTA Morphine CPP | | |
| Opiate Receptor Antagonist | | |
| Naloxone | Antagonism | (82) |
| D. Systemic (0.5 mg/kg) Morphine CPA | | |
| Opiate Receptor Antagonist | | |
| Methylnaltrexone | Antagonism | (15) |
| Lesions | | |
| Vagotomy | Antagonism | (12) |
| Visceral Cortex (6-OHDA) | Antagonism | (121) |
| E. Systemic Heroin CPP | | |
| Opiate Receptor Antagonist | | |
| Naloxone | Antagonism | (22,58) |
| DA Receptor Antagonists | | |
| Haloperidol | Antagonism | (104) |
| Pimozide | Antagonism | (22,58) |
| Alpha$_2$-adrenergic Agonist | | |
| Clonidine | Antagonism | (58) |
| Lesions | | |
| Intra-accumbens 6-OHDA | Antagonism | (104) |
| Peripheral NA Depletion | No effect | (104) |
| Central NA Depletion | No effect | (104) |
| F. ICV Dynorphin A [1–17] CPP | | |
| Opiate Receptor Antagonist | | |
| ICV Naloxone | Antagonism | (51) |
| DA Receptor Antagonists | | |
| SCH 23390 (D1 antagonist) | Antagonism | (52) |
| Spiroperidol (D2 antagonist) | Antagonism | (52) |
| G. ICV [D-Pen$^2$,D-Pen$^5$]-Enkephalin CPP | | |
| Delta Receptor Antagonist | | |
| ICI 174,864 (ICV) | Antagonism | (96) |
| H. Intra-VTA Thiorphan CPP | | |
| Opiate Receptor Antagonist | | |
| Intra-VTA Naloxone | Antagonism | (39) |

TABLE 2
CONTINUED

| Pretreatment | Effect | Reference |
|---|---|---|
| I. Intra-VTA [D-Ala$^2$]-Met$^5$-Enkephalinamide CPP | | |
| Opiate Receptor Antagonist | | |
| Naloxone | Antagonism | (83) |
| DA Receptor Antagonist | | |
| Haloperidol | Antagonism | (84) |
| Lesion | | |
| Ipsilateral LH (6-OHDA) | Antagonism | (84) |
| J. ICV Beta-endorphin CPP | | |
| Opiate Receptor Antagonist | | |
| Naloxone | Antagonism | (2) |
| K. Systemic Ketocyclazocine CPP | | |
| Opiate Receptor Antagonist | | |
| Naloxone | Antagonism | (49) |
| L. Systemic Ethylketocyclazocine CPP | | |
| Opiate Receptor Antagonist | | |
| Naloxone | Antagonism | (49) |
| M. Systemic Leu-Enkephalin CPP | | |
| Opiate Receptor Antagonist | | |
| Methylnaloxonium | Antagonism | (42) |
| N. Systemic U50,488 CPA | | |
| Kappa Receptor Antagonist | | |
| MR 2266 | Antagonism | (13) |
| Lesions | | |
| Arcuate Hypothalamus | No effect | (73) |
| Vagotomy | Produced CPP | (13) |
| O. Systemic U69,593 CPA | | |
| DA Receptor Antagonists | | |
| SCH 23390 (D1 antagonist) | Antagonism | (97,98) |
| Sulpiride (D2 antagonist) | No effect | (98) |
| Spiroperidol (D2 antagonist) | No effect | (98) |

The subheading (A, B, C, etc.) refers to the place conditioning effect (e.g., amphetamine-induced place preference); this is followed by a list of pretreatments and their effects on the place conditioning.

Abbreviations: AMPT: alpha-methyl-para-tyrosine; CPA: conditioned place aversion; CPP: conditioned place preference; DA: dopamine; DETC: diethyldithiocarbamate; 5,7-DHT: 5,7-dihydroxytryptamine; GABA: gamma-aminobutyric acid; 6-OHDA: 6-hydroxydopamine; ICV: intracerebroventricular; LH: lateral hypothalamus; mPFC: medial prefrontal cortex; NA: noradrenaline; VTA: ventral tegmental area.

properties of psychomotor stimulants. Microinjections of (+)-amphetamine or cocaine into this nucleus (5, 26, 27) resulted in a place preference (Table 1). Place conditioning was not obtained when amphetamine was microinjected into other areas containing dopaminergic terminals such as the medial prefrontal cortex (mPFC) (27), caudate nucleus (27), amygdala (27) or a region subjacent to the area postrema (27) (Table 1).

*State-dependent effects and the issue of novelty.* The motivational effects of novelty have been proposed as a possible explanation for drug-induced conditioned place preference (72). The logic is the rats always experience the conditioned environ-

ment in a drugged state; subsequently, in the test phase, the now drug-free animal may approach and spend more time on the conditioned side simply due to its perceived novelty. In fact, the importance of novelty in place conditioning has recently been demonstrated. Rats having only minimal exposure to one compartment during conditioning later showed a significant preference for that environment (25).

One way to rule out the novelty explanation for drug-induced place preference is to condition and test the animal in the same drugged state (72); if significant place conditioning is still observed, it suggests that the animals preferred the visual and tactile cues not because of their novelty but rather because of their previous association with the reinforcing properties of the drug. Tests of this nature have been conducted with cocaine, amphetamine, diazepam, quinpirole and SKF 38393, and with the exception of quinpirole, the conditioned effect was still apparent when the animals were treated with the drug during the test (45, 76, 105).

When rats were treated with quinpirole during the test, a significant place preference was no longer observed (45). According to the proposal of Mucha and Iversen (72), this suggests that in the original case, where animals were conditioned with quinpirole and tested drug-free, the animals approached and spent more time on the drug-paired side (during the test) because of its perceived novelty. However, in the study by Hoffman and Beninger (45), an additional group of animals which were never exposed to one of the compartments during conditioning failed to show a preference for this relatively novel environment during the test. Thus, novelty may not be an important element in the quinpirole-induced place preference, but whether the preference reflects reinforcing properties of the drug cannot be determined with certainty.

### *The Role of Dopaminergic Transmission*

By studying the effects of selective dopaminergic lesions or pretreatment with DA receptor antagonists, the role of DA in stimulant-induced place conditioning has largely been confirmed (Table 2). For example, pretreatment with haloperidol or alpha-flupenthixol during drug-environment pairings blocked the establishment of amphetamine-induced place conditioning (62, 67, 102), and the place preference produced by intra-accumbens amphetamine was inhibited when the active isomer of flupenthixol was coadministered with the drug (5).

In contrast, pretreatment with the DA receptor blockers alpha-flupenthixol, pimozide, or haloperidol failed to attenuate place conditioning produced by systemic injections of cocaine in rats (62, 68, 103). Spyraki *et al.* (103) attributed this failure to cocaine's local anesthetic properties. This suggestion was tenable because procaine, which has local anesthetic effects similar to cocaine but lacks the central stimulant action, produced a conditioned place preference (103).

Further support for this notion, as well as the idea that DA is important in cocaine's central stimulant effects, was obtained by Morency and Beninger (68). They observed that intracerebroventricular (ICV) injections of cocaine produced place conditioning which was blocked by pretreatment with systemically administered pimozide. ICV injections of procaine failed to produce place conditioning. The importance of the route of administration was also demonstrated by Spyraki, Nomikos and Varonos (107); cocaine-induced place conditioning was disrupted by haloperidol when cocaine was administered intravenously but not when it was administered intraperitoneally. Finally, place preference induced by intra-accumbens cocaine was inhibited when the active isomer of alpha-flupenthixol was coinjected with cocaine (5). Together these data suggest that central or intravenous administration of cocaine produces rewarding effects and these effects are DA-dependent.

The role of DA in psychomotor stimulant reward has also been confirmed by testing the effects of selective dopaminergic lesions produced by the neurotoxin 6-hydroxydopamine (6-OHDA) on the establishment of drug-induced place conditioning. Although Spyraki *et al.* (102) failed to observe an overall significant attenuation of amphetamine-induced place preference in rats with 6-OHDA lesions of the nucleus accumbens, there was a significant correlation between the DA levels in the nucleus accumbens and the magnitude of the place preference. Furthermore, DA depletion in the nucleus accumbens varied between 60 and 90 percent of controls, and the importance of a severe depletion of DA levels in attenuating a place preference effect has been demonstrated [cf. (84)].

Six-OHDA administered into the nucleus accumbens failed to prevent place conditioning established by systemic injections of cocaine (103). This may not be surprising given the previous failures of DA receptor antagonists to block place conditioning produced by *systemic* cocaine. DA receptor antagonists were effective when cocaine was injected centrally (or intravenously); therefore, similar lesions may block place conditioning induced by centrally administered cocaine.

There is one report implicating the mPFC in cocaine place conditioning; when this area was removed by suction, rats conditioned with subcutaneous injections of cocaine failed to show a place preference (48). This finding is interesting for two reasons. First, it implicates another region containing dopaminergic terminals in cocaine reinforcement; and second, because the place preference was no longer seen despite administering the cocaine systemically, it suggests that the local anesthetic properties of cocaine are either insufficient for the establishment of cocaine place preference or that lesions of the mPFC somehow minimize their effects on conditioning.

Apomorphine-induced place preference was significantly potentiated in rats with 6-OHDA lesions of the nucleus accumbens (109,114). Presumably postsynaptic DA receptor supersensitivity developed as a result of the lesion, and thus, apomorphine, a direct-acting DA receptor agonist, had a potentiated effect. The effect was blocked in rats with electrolytic lesions of the lateral preoptic area and substantia innominata, areas that receive a dense projection from the nucleus accumbens (109).

To date, the evidence suggests that DA may not be involved in mediating the reinforcing effects of the DA uptake inhibitors bupropion, methylphenidate, or nomifensine. DA receptor antagonists, in doses sufficiently large to block the locomotor stimulating effects of these uptake inhibitors, were ineffective in blocking the establishment of place conditioning (65, 67, 68). Six-OHDA administered into the lateral ventricles also failed to block methylphenidate-induced place preference (65). The reason for these failures is not known; the doses of DA blockers were probably sufficiently large, and it seems unlikely that noradrenergic mechanisms mediate the reinforcing effects of these stimulants because the noradrenaline (NA) uptake inhibitor desipramine failed to produce a place preference (65).

### *The Role of DA Receptor Subtypes*

Recent studies of the role of DA receptor subtypes suggest that both D1 and D2 receptors contribute to the establishment of amphetamine-induced place conditioning (Table 2). The selective D1 antagonist SCH 23390 or the D2 receptor antagonists metoclopramide or sulpiride attenuated amphetamine-induced place preference (24, 46, 59). Carr and Phillips (24) failed to block the amphetamine place preference in rats treated with metoclopramide, but only one dose of the antagonist was tested. Interestingly,

Gilbert *et al.* (38) observed a significant place preference when sulpiride was combined with a dose of amphetamine that alone produced no conditioning. The authors suggested that sulpiride facilitated the amphetamine place preference by preferentially blocking presynaptic autoreceptors thereby causing an increase in DA release. This finding and explanation, however, are inconsistent with the observation by Carr and Phillips (24) that sulpiride blocked amphetamine-induced place conditioning.

Subtype-selective antagonists tested on conditioning with the D1 agonist SKF 38393 or the D2 agonist quinpirole produced interesting results. The conditioned place aversion induced by SKF 38393 was dose-dependently attenuated by pretreating the animals with either metoclopramide or SCH 22390 (46). The effects of selective DA receptor antagonists on preference conditioning with quinpirole were more complicated. Although low to intermediate doses of SCH 23390 or metoclopramide inhibited the place preference, high doses of either antagonist were not effective (46). There doesn't appear to be a simple explanation for the lack of blockade with high doses.

### *The Role of Noradrenergic Transmission*

Noradrenergic pathways do no seem to be important for place preference conditioning with psychomotor stimulants (Table 2). Lesions that depleted peripheral NA failed to influence the establishment of place conditioning with amphetamine (102). Neither peripheral nor central NA depletion affected cocaine-induced place preference (103). However, because cocaine was injected intraperitoneally, it is difficult to draw definitive conclusions; it is not known, for example, if similar lesions would block conditioning produced by *central* injections of cocaine.

### *The Role of Serotonergic Transmission*

Recent studies testing the effects of altered serotonin (5-HT) transmission on the establishment of amphetamine-induced place preference are limited in number and the results are somewhat inconsistent (Table 2). For example, increasing serotonergic transmission with the 5-HT uptake inhibitor zimelidine antagonized the establishment of amphetamine-induced place preference (56). However, decreasing 5-HT transmission by pretreating the rats with the 5-$HT_2$ antagonist ritanserin also inhibited the preference (77). In contrast to the latter finding, neither serotonergic depletions of the nucleus accumbens nor treatment with 5-$HT_3$ antagonists affected the establishment of amphetamine place conditioning (23,106).

### *Summary*

Drugs that facilitate dopaminergic transmission produced conditioned place preferences. There was one exception to this generalization: the D1 agonist SKF 38393 resulted in a conditioned place aversion. At present, the reason for this is unknown; future tests with other D1 receptor agonists in combination with central microinjection techniques will provide information regarding the generality of the finding and the anatomical substrate. Furthermore, although the D2 agoninst quinpirole produced a place preference, the state-dependent nature of this effect questions the interpretation that the place preference reflected reinforcing properties of the drug.

The role of DA in mediating the reinforcing effects of psychomotor stimulants is well-supported, and at least in the case of amphetamine both D1 and D2 receptors seem to be important. Although originally it appeared that cocaine's reinforcing actions were not mediated by DA, subsequent studies revealed that the route of cocaine administration is an important variable: DA receptor antagonists were effective in blocking cocaine place preference only when the stimulant was admininstered intravenously or centrally, but not intraperitoneally. The explanation for these differential effects is that cocaine possesses local anesthetic properties that are sufficient for establishing place preference conditioning, and this place conditioning is independent of DA mechanisms.

Conditioned place preferences produced by the DA uptake inhibitors methylphenidate, nomifensine, or bupropion were not blocked by DA receptor antagonists. These observations represent a serious inconsistency with the DA hypothesis of drug reinforcement. Although these drugs are similar to cocaine in that they prevent the uptake of DA into the synaptic terminal, they do not share with cocaine (also a DA uptake inhibitor) local anesthetic properties; thus it seems unlikely that the route of drug administration would turn out to be an important variable for demonstrating that the reinforcing effects of these atypical stimulants are DA-dependent. Nevertheless, it is interesting that together these drugs share common pharmacological (i.e., block DA uptake) and behavioral profiles (i.e., inability of DA antagonists to block the place preference when the stimulant is administered IP), and perhaps the route of stimulant administration is important for reasons other than local anesthetic properties. To test this possibility, the effects of DA receptor antagonists on place preferences produced by *central* administration of these drugs should be evaluated.

The dopaminergic teminals located in the nucleus accumbens represent a critical anatomical substrate involved in the reinforcing effects of amphetamine. This area may be important for cocaine-induced place preference; firm conclusions await further study. The mPFC may also be important but only one place preference study has been conducted. Importantly, each of these substrates is consistent with an important role for DA because both areas receive dense dopaminergic projections from the ventral tegmental area (VTA).

Given the importance of the DA system, there is some interest in determining if DA receptor blockade alone produces place conditioning, perhaps even place aversions. In general, the evidence suggests that no conditioning occurs, however, exceptions have been reported.

For example, administration of the D1 antagonist SCH 23390 immediately prior to confinement in the environment resulted in a conditioned place aversion (97,98); in contrast, a 1-hr delay imposed between drug administration and confinement resulted in no effect (46). This failure to observe a place aversion is not due to metabolism of the drug because SCH 23390 is known to remain in the central nervous system bound to D1 receptors for several hours postinjection (92). Currently, there is no explanation for the discrepant results.

Perhaps even more puzzling was the place preference produced by the D2 receptor antagonist metoclopramide. It seems unlikely that the drug possesses reinforcing properties because it was *effective* in blocking the amphetamine-induced place preference (46), and reports of abuse have not been documented when the drug was used in treating gastrointestinal disorders in humans [cf. (41)]. Perhaps, the place preference paradigm is sensitive to aspects of drug action other than its rewarding effects. It has been predicted that drugs which decrease spontaneous motor activity will produce place preferences because of decreased exploration during conditioning; subsequently, during the test, the animals approach and spend more time on the drug-paired side because it is perceived as relatively novel (25). Although this could explain the preference observed with metoclopramide, it seems unlikely because SCH 23390 and other DA receptor antagonists decrease activity and yet fail to establish place preferences. Thus, the metoclopramide-induced place preference is an anomalous finding

that awaits further study. It is possible that conditioning with metoclopramide reflects unusual pharmacological features of the drug such as anticholinergic effects or preferential autoreceptor affinity.

Finally, the serotonergic system may provide another important link in the mediation of psychomotor stimulant reward, but the limited number of studies and perhaps inconsistent results prevent meaningful conclusions at this time.

## OPIATES

### *Effects of Opiate Agonists and Antagonists in the Place Conditioning Paradigm*

*Systemic administration.*

*Opiate agonists.* To date, there have been numerous reports demonstrating conditioned place preferences with morphine or heroin (Table 1). Only the active isomer of morphine was effective (71) and the place preferences produced by morphine or heroin were blocked in rats treated during conditioning with the opiate antagonist naloxone (7, 22, 49, 58, 74, 94) (Table 2). Because naloxone itself has been shown to produce place aversions (Table 1), blockade of morphine place preference may have resulted from a nonspecific aversive effect. Mucha *et al.* (74) addressed this possibility by pretreating rats with naloxone prior to both the morphine and saline pairing sessions; a significant antagonism was still observed.

Other opiate agonists etorphine and levorphanol (but not it's inactive isomer dextrorphan) produced place preferences (70,74). Intracerebral administration of the endogenous opioid peptides beta-endorphin and dynorphin A [1–17], and several enkephalin analogues resulted in conditioned place preferences (Table 1). These drug-induced place preferences were antagonized by naloxone pretreatment (2, 51, 83). A place preference was not observed with dynorphin A [2–17] a metabolite of dynorphin A [1–17] (51).

Systemic Leu-enkephalin resulted in a conditioned place preference or aversion depending on whether the drug was paired with the initially nonpreferred or preferred side of the apparatus (as determined in the preexposure phase prior to conditioning) (42). These effects are probably mediated peripherally because Leu-enkephalin does not readily cross the blood-brain barrier and the place preference was blocked by methylnaloxonium, a peripherally acting opiate antagonist (i.e., does not cross blood-brain barrier) (42). Also, ICV administration of Leu-enkephalin at two doses had no effect in the place conditioning paradigm (51).

Opiate receptors have been classified into three receptor subtypes: mu, delta, and kappa (64). The importance of each subtype to opiate-induced place preference was investigated by determining the effects of subtype-selective agonists in the place conditioning paradigm (Table 1).

Drugs that show preferential affinity for the mu receptor such as sufentanyl, fentanyl, and perhaps morphine resulted in conditioned place preferences (36,70) (Table 1). The effects were dose-dependent (10, 70, 98). Similarly, ICV administration of the delta agonist [D-Pen$^2$, D-Pen$^5$]-enkephalin resulted in a significant place preference which was blocked by the selective delta antagonist ICI 174,864 (96). Delta receptors may not mediate the reinforcing effects of morphine, however, as several doses of ICI 174,864 did not modify morphine-induced place preference (96).

The results obtained with kappa agonists appear to be more complicated. Rats conditioned with bremazocine [or its active isomer (−)-bremazocine], U69,593, or U50,488 consistently showed an aversion to the drug-paired environment (13, 49, 70, 73, 97, 98). On the other hand, other kappa agonists have been shown to produce conditioned place preferences. Slight, but nonsignificant, preferences were observed with the drugs ethylketocyclazocine and trifluadom (70), and Iwamoto (49) found significant dose-dependent place preferences with ethylketocyclazocine as well as ketocyclazocine, each of which were blocked with the opiate antagonist naloxone. The kappa agonist Mr 2034, in the dose range tested, had no effect (70).

Bechara and van der Kooy (12) suggested that the aversion produced by some kappa agonists may result from stimulation of peripheral kappa receptors on the primary sensory neurons. Evidence for a peripherally mediated aversive effect of opiates is suggested by several findings. First, increasing doses of the peripherally acting opiate antagonist methylnaltrexone (particularly when administered IP) produced conditioned place preferences (12). Second, a low dose of naltrexone (0.1 mg/kg IP) produced a place preference whereas a low dose of morphine (0.05 mg/kg IP) was shown to induce a significant place aversion (12, 15, 121). These effects may result from locally blocking or stimulating, respectively, the opiate receptors in the gut; the doses are low enough that significant stimulation of the central receptors may not occur. In support of this, the place aversion produced by morphine was blocked by methylnaltrexone (15) or vagotomy (12), and similarly, the place preference produced by naloxone was blocked by vagotomy (12).

Preliminary evidence obtained from the same laboratory implicated the kappa receptor in mediating these peripherally mediated aversive effects of opiates. They, like others, observed a place aversion in rats conditioned with the kappa agonist U50,488, and in addition, the kappa antagonist Mr2266 at low doses produced conditioned place preferences (13). In vagotomized rats, a dose of U50,488, which in sham-operated animals produced no effect, resulted in a significant place preference (13)!

Although the evidence is preliminary, kappa receptors in the *periphery* may mediate the aversive effects of opiates and kappa receptors in the brain may mediate in part the rewarding effects of opiates. The latter suggestion is based on the observation that a kappa agonist resulted in a place preference in vagotomized animals. In addition, Iwamoto (51) discovered that ICV administration of dynorphin A [1–17] produced a place preference, and because only a high dose of naloxone blocked the effect, he suggested that the preference was mediated by kappa receptors.

If there exist separate anatomical systems mediating aversive and rewarding effects of opiates, and if kappa receptors are involved in each system, then the divergent effects of kappa agonists are explainable. Perhaps the dose and efficiency of the drug in penetrating the blood-brain barrier are important variables that influence the relative stimulation of peripheral versus central receptors, and this in turn determines whether a preference or aversion will result from kappa agonists. Studies investigating the effects of centrally administered kappa agonists in the place conditioning paradigm would be useful in addressing this hypothesis.

*Opiate antagonists.* Conditioned place aversions produced by the opiate antagonists naloxone or naltrexone have been demonstrated in naive and morphine-dependent animals (Table 1). Failures to observe place aversions have been documented but in some cases the animals received only one drug-environment pairing (7,69), and in other studies (22,83), the drug was paired with the initially nonpreferred compartment thus making a further reduction in the amount of time spent in this compartment from pre- to post-conditioning less probable.

The aversiveness of antagonists appears to be centrally mediated because neither vagotomy nor methylnaltrexone blocked the aversion (12,15). Furthermore, systemic administration of peripherally acting opiate antagonists was reported to produce either no effect (40,42) or in some cases a preference (12), and when administered centrally, an aversion was obtained (40). The failure of Mucha (69) to observe an aversion with ICV methylnaltrexone may be because there was only one drug-environment pairing.

The aversive effects of naloxone may result from blocking receptors for endogenous beta-endorphin; lesions of the mediobasal arcuate hypothalamus, the main region containing beta-endorphin cell bodies, inhibited the establishment of naloxone-induced place aversion without affecting morphine-induced place preference (73). The place aversion produced by U50,488 was not affected by the lesions; this is consistent with the notion that the aversive effects of kappa agonists are mediated peripherally.

*Central administration.* Morphine-induced place preferences appear to be centrally mediated because neither neonatal capsaicin treatment (which destroys sensory neurons) nor vagotomy blocked the establishment of this conditioning (12,15).

Several attempts have been made to isolate the brain region(s) responsible for mediating the reinforcing effects of opiate agonists; there is some evidence that areas rich in dopaminergic cell bodies or terminals may be involved (Table 1). Unilateral injection of the enkephalinase inhibitor thiorphan into the VTA produced conditioned place preference which was blocked when naloxone was coinjected with thiorphan (39). Bilateral injections of morphine into the VTA, but not 2.5 mm dorsal to this area, produced a conditioned place preference in rats (82). Furthermore, Bozarth (20) mapped the rostral-caudal and ventral bounderies of the VTA where unilateral microinjections (250 ng) were effective in producing place preferences; the effective region corresponded to the area containing the mesolimbic DA cell bodies.

Several other regions support opiate-induced conditioned place preferences (Table 1). van der Kooy *et al.* (113) obtained place conditioning when morphine (5 micrograms, bilaterally) was microinjected directly into the lateral hypothalamus (LH), periaqueductal gray (PAG) or nucleus accumbens of rats. A place preference was also observed when morphine (20 micrograms) was unilaterally injected into the hippocampus (29). Because different doses and conditioning procedures were used, it is difficult to determine if one site is more critical than another in mediating the reinforcing actions of opiates. A systematic comparison of several doses of morphine across several brain regions using the same conditioning procedure would be useful in identifying the *critical* brain areas.

As an aside, the pendunculopontine nucleus may be another important link in the establishment of morphine place preference; ibotenic acid lesions of this nucleus were found to block morphine place preference (14).

*State-dependent effects and the issue of novelty.* The possibility that novelty effects may contribute to drug-induced place conditioning was discussed above. As with psychomotor stimulants, novelty is an inadequate explanation for opiate-induced place preferences. Animals that were conditioned and tested in the same drugged state with either morphine (72,96) or the delta agonist [D-Pen$^2$, D-Pen$^5$]-enkephalin (96) still showed significant place preference conditioning.

### *The Role of Dopaminergic Transmission*

Biochemical and behavioral evidence suggests that opiates stimulate the release of DA. Brain microdialysis studies have shown that opiates with preferential affinity for the mu receptor (e.g., morphine and fentanyl) increased synaptic DA concentration in the nucleus accumbens of freely moving rats (32). In contrast, the kappa agonists U50,488 and bremazocine caused a decrease in synaptic DA concentrations in both the caudate and nucleus accumbens. This latter effect of may provide an alternative explanation (see above) for the place aversions observed with U50,488 and bremazocine.

Behavioral evidence for DA involvement in opiate reward comes from determining the effects of selective DA receptor blockade or DA depletions on opiate-induced place preference (Table 2). For example, heroin- or morphine-induced place conditioning was antagonized by pretreatment with the DA receptor blockers pimozide or haloperidol, respectively (22, 58, 59, 93, 104). In contrast, Mackey and van der Kooy (62) failed to affect morphine-induced place conditioning when animals were pretreated during conditioning with alpha-flupenthixol or haloperidol, yet the same doses of antagonists blocked amphetamine-induced place preference. The reason for this inconsistency is not known.

Unilateral injections of enkephalin into the VTA produced a conditioned place preference that was significantly attenuated by systemic injections of haloperidol (84). In the same study, lesions of the ascending dopaminergic pathway (by injecting 6-OHDA at the level of the lateral hypothalamus) disrupted place conditioning when the lesion was ipsilateral to the site of the central enkephalin injection and resulted in a greater than 90 percent depletion of forebrain DA levels. Finally, Spyraki *et al.* (104) observed that bilateral 6-OHDA lesions of the nucleus accumbens attenuated heroin-induced place conditioning. Together, these studies implicate an important role for DA in opiate reward.

The peripherally mediated aversive effects of opiates may be processed centrally by DA in the visceral cortex. Six-OHDA lesions of this area disrupted morphine-induced place aversions (121), but not morphine-induced place preferences (121).

### *The Role of DA Receptor Subtypes*

Recent studies investigating the role of DA receptor subtypes in the establishment of opiate place conditioning have demonstrated an important role for the D1 receptor; the role of the D2 receptor remains unclear (Table 2). In the case of morphine, the D1 antagonist SCH 23390 blocked conditioning (59, 97, 98). Importantly, the potentially aversive properties of SCH 23390 were controlled by administering the antagonist on both saline- and drug-pairing days. In contrast, the preferential D2 antagonists sulpiride and spiroperidol failed to affect morphine place preference (98); however, only one dose of each antagonist was tested and the time delay between sulpiride treatment and conditioning may not have been sufficiently long [cf. (61)]. With ICV dynorphin A [1–17], both SCH 23390 and spiroperidol blocked the place preference (52). Thus, the effects of SCH 23390 on opiate-induced place conditioning are consistent and implicate a role for the D1 receptor. The D2 receptor may also be involved but further studies with other opiates and D2 antagonists are required.

Place aversions resulting from naloxone or the kappa agonist U69,593 but not the aversion produced by lithium chloride were also disrupted by SCH 23390 (97,98) suggesting an important role for the D1 receptor. Neither sulpiride nor spiroperidol blocked the place aversions produced by U69,593 or naloxone, but again only one dose of each antagonist was tested (98).

### *The Role of Noradrenergic Transmission*

With the exception of one finding, the evidence suggests that NA does not play an important role in opiate-induced place conditioning (Table 2). Peripheral or central noradrenergic depletions did not affect place preferences induced by heroin or morphine (93,104). Similarly pretreatment with the dopamine-beta-hydroxylase inhibitor diethyldithiocarbamate (DETC) had no effect on morphine-place conditioning (93).

In contrast to the above findings, LeMoal *et al.* (58) found that the alpha$_2$-adrenergic agonist clonidine inhibited place preference conditioning with heroin. Interestingly, when clonidine was given alone, a place preference was observed (3).

### *The Role of Serotonergic Transmission*

In general, the evidence suggests that intact serotonergic

transmission is important for the establishment of morphine-induced place preference (Table 2). Systemic administration of 5-$HT_2$ or 5-$HT_3$ receptor antagonists disrupted morphine place conditioning (23,77) as did selective 5-HT lesions of the nucleus accumbens (106). In contrast to these findings, 5-HT depletion, achieved with the tryptophan hydroxylase inhibitor p-chlorophenylalanine, failed to disrupt acquisition of morphine-induced place preference (93); the large dose of morphine (20 mg/kg) and the fact that the animals received several injections of morphine prior to conditioning (93) may explain this inconsistent observation.

Increasing serotonergic transmission with the uptake inhibitor zimelidine failed to affect morphine place conditioning (56). This contrasts with amphetamine place conditioning where zimelidine inhibited the place preference (56).

*Summary*

Systemic administration of opiate agonists produced conditioned place preferences. Mu and delta receptors are likely involved, but the role of kappa receptors remains unclear. Findings from Bechara and van der Kooy (12,13) suggest that peripheral kappa receptors mediate aversive effects of opiates while central kappa receptors contribute in part to their reinforcing effects. These two opposing functions may explain the inconsistent results observed with kappa agonists in the place conditioning paradigm.

As noted above, DA appears to be involved in mediating the reinforcing effects of opiates: DA receptor antagonists and selective depletions of central DA prevented the establishment of opiate place preferences. Studies employing DA antagonists selective for one receptor subtype have pointed to the importance of the D1 receptor but the data so far are insufficient regarding the role of the D2 receptor. There was one exception to these findings that has implicated an important role for DA. Mackey and van der Kooy (62) failed to block morphine place conditioning in rats treated with alpha-flupenthixol or haloperidol. The reason for this discrepancy is not known.

Employing microinjection techniques, it appears that one of the anatomical substrates for opiate reward is the dopaminergic cell bodies of the mesolimbic system located in the VTA. Opiate receptors in other areas such as the hippocampus, nucleus accumbens, LH and PAG seem to be important as well. Systematic studies comparing the effectiveness of opiate agonists over a wide range of doses in various brain regions are needed to determine the relative importance of each site and to map the neural circuitry mediating opiate reinforcement. At this time, it is not known if there exists a *single* reward circuit with the different sites supporting place conditioning connected in series or if there exist *multiple* opiate reward circuits organized in parallel with one another.

In addition to the prominent role of DA, 5-HT systems may also be involved in the neural circuitry of opiate conditioned place preference. Destruction or reversible blockade of 5-HT transmission interferes with the establishment of morphine place conditioning. The generalization of this result to other opiates awaits further study.

Finally, blockade of endogenous opioid systems is aversive; animals conditioned with opiate antagonists demonstrated place aversions and this effect appears to be centrally mediated. Interestingly, this was not the case when central DA systems were blocked.

## CONCLUSIONS

A large body of evidence suggests that DA is involved in mediating the behavioral effects of reinforcing stimuli. In the past, much of the evidence was based on the observation that DA receptor antagonists disrupted behavior that was controlled by a reinforcing stimulus such as food-reinforced lever-pressing. However, because DA receptor antagonists also suppress locomotor activity and induce catalepsy, it was difficult to establish if DA blockers disrupted the food-reinforced lever pressing by producing a nonspecific motor impairment or by directly affecting reward mechanisms.

Procedures based on the conditioned reinforcement principle such as the place conditioning paradigm were adopted at least in part because they minimize this problem. In the place conditioning paradigm, DA receptor antagonists are administered *only* during the conditioning phase of the experiment (food-environment pairings) when response demands are minimal. The evidence of conditioning or lack of conditioning is obtained from subsequent testing sessions when the animal is drug-free and thus unaffected by any performance-limiting consequences of the DA blockers.

This technique is particularly well-suited for studying the neuropharmacology of drug reward. In this case, evidence for the reinforcing actions of a drug is determined in an animal that is drug-free, and furthermore, the effects of pharmacological challenges (e.g., DA receptor antagonists) on drug reward are determined by administering the challenge during conditioning (drug-environment pairings) and only later testing for potential conditioning in a drug-free animal.

This procedure has proven successful in demonstrating the reinforcing properties of psychomotor stimulants and opiates, and there has been considerable progress in isolating the anatomical and pharmacological substrates of these effects. The hypothesis that DA, particularly within the mesolimbic system, plays an important role in opiate and psychomotor stimulant reward continues to gain support.

Despite progress in understanding the chemical and anatomical substrates of drug reward, there remains a number of unanswered questions. For example, the preferential D1 receptor agonist SKF 38393 produced a place aversion. This result is unusual given the place preferences established by other dopaminergic agonists (Table 1). The SKF 38393-induced aversion is also inconsistent with the finding that the D1 receptor antagonist SCH 23390 disrupted the establishment of amphetamine- or morphine-induced place preference. SKF 38393 is a partial agonist for the D1 receptor and this property may influence its behavioral effects. Clearly, studying the effects of other D1 agonists, administered peripherally as well as centrally, will provide further insight into this anomalous finding.

The failure of DA receptor antagonists in blocking place preferences produced by methylphenidate, nomifensine, or bupropion is inconsistent with a DA hypothesis of drug reward. Using central microinjection techniques to map the anatomical substrate(s) underlying place preferences produced by these stimulants may provide valuable information. Furthermore, testing the effects of antagonists selective for neurotransmitter systems other than DA requires investigation.

Interestingly, in addition to DA, intra-accumbens 5-HT may play an important role in drug reward. Selective 5-$HT_3$ antagonists or selective serotonergic lesions of the nucleus accumbens disrupted morphine but not amphetamine place conditioning. Moreover, facilitation of 5-HT transmission with the uptake inhibitor zimiledine blocked amphetamine but not morphine place preference. These data suggest an interesting dissociation in the role of 5-HT in opiate and psychomotor stimulant reward, but the data are still preliminary. Furthermore, when a selective 5-$HT_2$ antagonist was tested, both morphine and amphetamine place conditioning was inhibited, thus, a dissociation of serotonin's role may not generalize to 5-$HT_2$ receptors.

Stimulation of central mu receptors, and perhaps delta receptors, contribute to the reinforcing effects of opiates. The contri-

bution of kappa receptors remains unclear. Because of the possibility that stimulation of peripheral kappa receptors is aversive, the optimal approach for determining the role of central kappa receptors is to test the effects of intracranial kappa agonists in the place conditioning paradigm.

One anatomical site of opiate reward appears to be the dopaminergic cell bodies of the VTA. Yet other regions of the brain such as the hippocampus, nucleus accumbens, LH, and PAG also support opiate-induced conditioned place preference. The pendunculopontine nucleus may be another important nucleus involved in opiate place conditioning. It is not known if these various sites are arranged in series as part of one neural circuit or whether there are separate anatomical pathways arranged in parallel all of which mediate opiate reward. In any event, the relative contributions of each site within drug reward awaits further study.

ACKNOWLEDGEMENT

I wish to thank Dr. Roy A. Wise for his critical comments and suggestions on earlier drafts of this manuscript.

## REFERENCES

1. Advocat, C. Evidence of place conditioning after chronic intrathecal morphine in rats. Pharmacol. Biochem. Behav. 22:271–277; 1985.
2. Amalric, M.; Cline, E. J.; Martinez, J. L., Jr.; Bloom, F. E.; Koob, G. F. Rewarding properties of β-endorphin as measured by conditioned place preference. Psychopharmacology (Berlin) 91:14–19; 1987.
3. Asin, K. E.; Wirtshafter, D. Clonidine produces a conditioned place preference in rats. Psychopharmacology (Berlin) 85:383–385; 1985.
4. Asin, K. E.; Wirtshafter, D.; Tabakoff, B. Failure to establish a conditioned place preference with ethanol in rats. Pharmacol. Biochem. Behav. 22:169–173; 1985.
5. Aulisi, E. F.; Hoebel, B. G. Rewarding effects of amphetamine and cocaine in the nucleus accumbens and block by flupenthixol. Soc. Neurosci. Abstr. 9:121; 1983.
6. Bardo, M. T.; Miller, J. S.; Neisewander, J. L. Conditioned place preference with morphine: The effect of extinction training on the reinforcing CR. Pharmacol. Biochem. Behav. 21:545–549; 1984.
7. Bardo, M. T.; Neisewander, J. L. Single-trial conditioned place preference using intavenous morphine. Pharmacol. Biochem. Behav. 25:1101–1105; 1986.
8. Bardo, M. T.; Neisewander, J. L. Chronic naltrexone supersensitizes the reinforcing and locomotor-activating effects of morphine. Pharmacol. Biochem. Behav. 28:267–273; 1987.
9. Bardo, M. T.; Neisewander, J. L.; Miller, J. S. Repeated testing attenuates conditioned place preference with cocaine. Psychopharmacology. (Berlin) 89:239–243; 1986.
10. Barr, G. A.; Paredes, W.; Bridger, W. H. Place conditioning with morphine and phencyclidine: dose dependent effects. Life Sci. 36:363–368; 1985.
11. Beach, H. D. Morphine addiction in rats. Can. J. Psychol. 11: 104–112; 1957.
12. Bechara, A.; van der Kooy, D. Opposite motivational effects of endogenous opioids in brain and periphery. Nature 314:533–534; 1985.
13. Bechara, A.; van der Kooy, D. Kappa receptors mediate the peripheral aversive effects of opiates. Pharmacol. Biochem. Behav. 28:227–233; 1987.
14. Bechara, A.; van der Kooy, D. The incentive motivational properties of food and opiates are mediated by a common brainstem substrate. Soc. Neurosci. Abstr. 14:1103; 1988.
15. Bechara, A.; Zito, K. A.; van der Kooy, D. Peripheral receptors mediate the aversive conditioning effects of morphine in the rat. Pharmacol. Biochem. Behav. 28:219–225; 1987.
16. Beninger, R. J. The role of dopamine in locomotor activity and learning. Brain Res. Rev. 6:173–196; 1983.
17. Beninger, R. J.; Phillips, A. G. The effects of pimozide in the establishment of conditioned reinforcement. Psychopharmacology (Berlin) 68:147–153; 1980.
18. Best, P. J.; Best, M. R.; Mickley, G. A. Conditioned aversion to distinct environmental stimuli resulting from gastrointestinal distress. J. Comp. Physiol. Psychol. 85:250–257; 1973.
19. Blander, A.; Hunt, T.; Blair, R.; Amit, Z. Conditioned place preference: An evaluation of morphine's positive reinforcing properties. Psychopharmacology (Berlin) 84:124–127; 1984.
20. Bozarth, M. A. Neuroanatomical boundaries of the reward-relevant opiate-receptor field in the ventral tegmental area as mapped by the conditioned place preference method in rats. Brain Res. 414:77–84; 1987.
21. Bozarth, M. A. Conditioned place preference: A parametric analysis using systemic heroin injections. In: Bozarth, M. A., ed. Methods of assessing the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987:241–273.
22. Bozarth, M. A.; Wise, R. A. Herion reward is dependent on a dopaminergic substrate. Life Sci. 29:1881–1886; 1981.
23. Carboni, E.; Acquas, E.; Leone, P.; DiChiara, G. $5HT_3$ receptor antagonists block morphine- and nicotine- but not amphetamine-induced reward. Psychopharmacology (Berlin) 97:175–178; 1989.
24. Carr, G. D.; Phillips, A. G. Differential effects of dopamine antagonists on amphetamine-induced locomotor stimulation and reward. Soc. Neurosci. Abstr. 13:833; 1987.
25. Carr, G. D.; Phillips, A. G.; Fibiger, H. C. Independence of amphetamine reward from locomotor stimulation demonstrated by conditioned place preference. Psychopharmacology (Berlin) 94: 221–6; 1988.
26. Carr, G. D.; White, N. M. Conditioned place preference from intra-accumbens but not intra-caudate amphetamine injections. Life Sci. 33:2551–2557; 1983.
27. Carr, G. D.; White, N. M. Anatomical disassociation of amphetamine's rewarding and aversive effects: an intracranial microinjection study. Psychopharmacology (Berlin) 89:340–346; 1986.
28. Clarke, P. B. S.; Fibiger, H. C. Apparent absence of nicotine-induced conditioned place preference in rats. Psychopharmacology (Berlin) 92:84–88; 1987.
29. Corrigall, W. A.; Linseman, M. A. Conditioned place preference produced by intra-hippocampal morphine. Pharmacol. Biochem. Behav. 30:787–789; 1988.
30. Costello, N. L.; Carlson, J. N.; Glick, S. D. Dose-dependent and baseline-dependent conditioning in the place preference paradigm. Soc. Neurosci. Abstr. 13:998; 1987.
31. Davis, W. M.; Smith, S. G. Catecholaminergic mechanisms of reinforcement: direct assessment of drug self-administration. Life Sci. 20:483–492; 1977.
32. DiChiara, G.; Imperato, A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. USA 85:5274–5278; 1988.
33. Di Scala, G.; Martin-Iverson, M. T.; Phillips, A. G.; Fibiger, H. C. The effects of progabide (SL 76002) on locomotor activity and conditioned place preference induced by d-amphetamine. Eur. J. Pharmacol. 107:271–274; 1985.
34. Dymshitz, J.; Lieblich, I. Opiate reinforcement and naloxone aversion as revealed by place preference paradigm, in two strains of rats. Psychopharmacology (Berlin) 92:473–477; 1987.
35. Ettenberg, A.; Duvauchelle, C. L. Haloperidol blocks the conditioned place preferences induced by rewarding brain stimulation. Behav. Neurosci. 102:687–691; 1988.
36. Finlay, J. M.; Jakubovic, A.; Phillips, A. G.; Fibiger, H. C. Fentanyl-induced conditional place preference: lack of associated conditional neurochemical events. Psychopharmacology (Berlin) 96:534–540; 1988.
37. Gilbert, D.; Cooper, S. J. Beta-phenylethylamine-, d-amphetamine- and l-amphetamine-induced place preference conditioning in rats. Eur. J. Pharmacol. 95:311–314; 1983.
38. Gilbert, D. B.; Dembski, J. E.; Stein, L.; Belluzzi, J. D. Dopamine and reward: conditioned place preference induced by dopamine D2

receptor agonist. Soc. Neurosci. Abstr. 12:938; 1986.
39. Glimcher, P. W.; Giovino, A. A.; Margolin, D. H.; Hoebel, B. G. Endogenous opiate reward induced by an enkephalinase inhibitor, thiorphan, injected into the ventral midbrain. Behav. Neurosci. 98:262–268; 1984.
40. Hand, T. H.; Koob, G. F.; Stinus, L.; LeMoal, M. Aversive properties of opiate receptor blockade: evidence for exclusively central mediation in naive and morphine-dependent rats. Brain Res. 474:364–388; 1988.
41. Harrington, R. A.; Hamilton, C. W.; Brogden, R. N.; Linkewich, J. A.; Romankiewicz, J. A.; Heel, R. C. Metoclopramide: An updated review of its pharmacological properties and clinical use. Drugs 25:451–494; 1983.
42. Heinrichs, S. C.; Martinez, J. L., Jr. Modification of place preference conditioning in mice by systematically administered [Leu]enkephalin. Behav. Brain Res. 22:249–255; 1986.
43. Hiroi, N.; White, N. M. Effects of alpha-methyl-para-tyrosine on the maintenance of conditioned place preference. Soc. Neurosci. Abstr. 14:850; 1988.
44. Hoffman, D. C.; Beninger, R. J. The effects of pimozide on the establishment of conditioned reinforcement as a function of the amount of conditioning. Psychopharmacology (Berlin) 87:454–460; 1985.
45. Hoffman, D. C.; Beninger, R. J. Selective D1 and D2 dopamine agonists produce opposing effects in place conditioning but not conditioned taste aversion learning. Pharmacol. Biochem. Behav. 31:1–8; 1988.
46. Hoffman, D. C.; Beninger, R. J. The effects of selective dopamine D1 or D2 receptor antagonists on the establishment of agonist-induced place conditioning. Pharmacol. Biochem. Behav. 33:273–279; 1989.
47. Hoffman, D. C.; Dickson, P. R.; Beninger, R. J. The dopamine D2 receptor agonists quinpirole and bromocriptine produce conditioned place preferences. Prog. Neuropsychopharmacol. Biol. Psychiatry 12:315–322; 1988.
48. Issac, W.; Neisewander, J.; Landers, T.; Alcala, R.; Bardo, M.; Nonneman, A. Mesocortical dopamine system lesions disrupt cocaine reinforced conditioned place preference. Soc. Neurosci. Abstr. 10:1206; 1984.
49. Iwamoto, E. T. Place-conditioning properties of mu, kappa, and sigma opioid agonists. Alcohol Drug Res. 6:327–339; 1986.
50. Iwamoto, E. T. Place-aversion conditioned by phencyclidine in rats: development of tolerance and pharmacologic antagonism. Alcohol Drug Res. 6:265–276; 1986.
51. Iwamoto, E. T. Dynorphin A [1–17] induces "reward" in rats in the place conditioning paradigm. Life Sci. 43:503–508; 1988.
52. Iwamoto, E. T. Dynorphin A [1–17] place preference in rats: opioid-specific and dopaminergic. Soc. Neurosci. Abstr. 14:293; 1988.
53. Katz, R. J.; Gormezano, G. A rapid and inexpensive technique for assessing the reinforcing effects of opiate drugs. Pharmacol. Biochem. Behav. 11:213–233; 1979.
54. Kebabian, J. W.; Calne, D. B. Multiple receptors for dopamine. Nature 277:93–96; 1979.
55. Kelsey, J. E.; Carlezon, W. A., Jr.; Falls, W. A. Lesions of the nucleus accumbens in rats reduce opiate reward, but not tolerance. Soc. Neurosci. Abstr. 13:424; 1987.
56. Kruszewska, A.; Romandini, S.; Samanin, R. Different effects of zimelidine on the reinforcing properties of d-amphetamine and morphine on conditioned place preference in rats. Eur. J. Pharmacol. 125:283–286; 1986.
57. Kumar, R. Morphine dependence in rats: secondary reinforcement from environmental stimuli. Psychopharmacologia 25:332–338; 1972.
58. LeMoal, M.; Stinus, L.; Hand, T. H. Different mechanisms underlie the acquisition and expression of heroin-induced place preference. Soc. Neurosci. Abstr. 14:661; 1988.
59. Leone, P.; Di Chiara, G. Blockade of D-1 receptors by SCH 23390 antagonizes morphine- and amphetamine-induced place preference conditioning. Eur. J. Pharmacol. 135:251–254; 1987.
60. Lett, B. T. Enhancement of conditioned preference for a place paired with amphetamine produced by blocking the association between place and amphetamine-induced sickness. Psychopharmacology (Berlin) 95:390–394; 1988.
61. Ljungberg, T. Blockade by neuroleptics of water intake and operant responding for water in the rat: Anhedonia, motor deficit, or both? Pharmacol. Biochem. Behav. 27:341–350; 1987.
62. Mackey, W. B.; van der Kooy, D. Neuroleptics block the positive reinforcing effects of amphetamine but not of morphine as measured by place conditioning. Pharmacol. Biochem. Behav. 22:101–105; 1985.
63. Martin, G. M.; Bechara, A.; van der Kooy, D. Morphine preexposure attenuates the aversive properties of opiates without preexposure to the aversive properties. Pharmacol. Biochem. Behav. 30:687–692; 1988.
64. Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. The effect of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J. Pharmacol. Exp. Ther. 197:517–532; 1976.
65. Martin-Iverson, M. T.; Ortmann, R.; Fibiger, H. C. Place preference conditioning with methylphenidate and nomifensine. Brain Res. 332:59–67; 1985.
66. Michaelis, R. C.; Holloway, F. A.; Harland, R. D.; Criado, J. R. Conditioned place preference for cocaine in rats: open test with known expected baseline choice values. Soc. Neurosci. Abstr. 13:1719; 1987.
67. Mithani, S.; Martin-Iverson, M. T.; Phillips, A. G.; Fibiger, H. C. The effects of haloperidol on amphetamine and methylphenidate-induced conditioned place preferences and locomotor activity. Psychopharmacology (Berlin) 90:247–252; 1986.
68. Morency, M. A.; Beninger, R. J. Dopaminergic substrates of cocaine-induced place conditioning. Brain Res. 399:33–41; 1987.
69. Mucha, R. F. Is the motivational effect of opiate withdrawal reflected by common somatic indices of precipitated withdrawal? A place conditioning study in the rat. Brain Res. 418:214–220; 1987.
70. Mucha, R. F.; Herz, A. Motivational properties of kappa and mu opioid receptor agonists studied with place and taste preference conditioning. Psychopharmacology (Berlin) 86:274–280; 1985.
71. Mucha, R. F.; Herz, A. Preference conditioning produced by opioid active and inactive isomers of levorphanol and morphine in rat. Life Sci. 38:241–249; 1986.
72. Mucha, R. F.; Iversen, S. D. Reinforcing properties of morphine and naloxone revealed by conditioned place preferences: A procedural examination. Psychopharmacology (Berlin) 82:241–247; 1984.
73. Mucha, R. F.; Millan, M. J.; Herz, A. Aversive properties of naloxone in non-dependent (naive) rats may involve blockade of central beta-endorphin. Psychopharmacology (Berlin) 86:281–285; 1985.
74. Mucha, R. F.; van der Kooy, D.; O'Shaughnessy, M.; Bucenieks, P. Drug reinforcement studies by the use of place conditioning in rat. Brain Res. 243:91–105; 1982.
75. Mucha, R. F.; Walker, M. J. K. Aversive property of opioid receptor blockade in drug-naive mice. Psychopharmacology (Berlin) 93: 483–488; 1987.
76. Nomikos, G. G.; Spyraki, C. Cocaine-induced place conditioning: importance of route of administration and other procedural variables. Psychopharmacology (Berlin) 94:119–125; 1988.
77. Nomikos, G. G.; Spyraki, C. Effects of ritanserin on the rewarding properties of d-amphetamine, morphine and diazepam revealed by conditioned place preference in rats. Pharmacol. Biochem. Behav. 30:853–858; 1988.
78. Ortmann, R. The conditioned place preference paradigm in rats: effect of bupropion. Life Sci. 37:2021–2027; 1985.
79. Papp, M. Different effects of short- and long-term treatment with imipramine on the apomorphine- and food-induced place preference conditioning in rats. Pharmacol. Biochem. Behav. 30:889–893; 1988.
80. Pavlov, I. P. Conditioned reflexes. Oxford: Oxford University Press; 1927.
81. Pettit, H. O.; Mueller, K. VTA microinjections of (S)-cholecystokinin octapeptide potentiate amphetamine conditioned place preferences. Soc. Neurosci. Abstr. 13:612; 1987.
82. Phillips, A. G.; LePiane, F. G. Reinforcing effects of morphine microinjection into the ventral tegmental area. Pharmacol. Biochem. Behav. 12:965–968; 1980.
83. Phillips, A. G.; LePiane, F. G. Reward produced by microinjection

of (D-Ala$^2$), Met$^5$-enkephalinamide into the ventral tegmental area. Behav. Brain Res. 5:225–229; 1982.
84. Phillips, A. G.; LePiane, F. G.; Fibiger, H. C. Dopaminergic mediation of reward produced by direct injection of enkephalin into the ventral tegmental area of the rat. Life Sci. 33:2505–2511; 1983.
85. Reicher, M. A.; Holman, E. W. Location preference and flavour aversion reinforced by amphetamine in rats. Anim. Learn. Behav. 5:343–346; 1977.
86. Rossi, N. A.; Reid, L. D. Affective states associated with morphine injections. Physiol. Psychol. 4:269–274; 1976.
87. Sanberg, P. R.; Bunsey, M. D.; Giordano, M.; Norman, A. B. The catalepsy test: its ups and downs. Behav. Neurosci. 102:748–759; 1988.
88. Schenk, S.; Ellison, F.; Hunt, T.; Amit, Z. An examination of heroin conditioning in preferred and nonpreferred environments and in differentially housed mature and immature rats. Pharmacol. Biochem. Behav. 22:215–220; 1985.
89. Schenk, S.; Hunt, T.; Colle, L.; Amit, Z. Isolation versus grouped housing: differential effects of low doses of heroin in the place preference paradigm. Life Sci. 32:1129–1134; 1983.
90. Schenk, S.; Hunt, T.; Malovechko, R.; Robertson, A.; Klukowski, G.; Amit, Z. Differential effects of isolation housing on the conditioned place preference produced by cocaine and amphetamine. Pharmacol. Biochem. Behav. 24:1793–1796; 1986.
91. Schneirla, T. C. An evolutionary and developmental theory of biphasic processes underlying approach and withdrawal. In: Jones, M. R., ed. Nebraska symposium on motivation. Lincoln: University of Nebraska Press; 1959:1–42.
92. Schultz, D. W.; Staples, L.; Mailman, R. B. SCH 23390 causes persistent antidopaminergic effects in vivo: evidence for longterm occupation of receptors. Life Sci. 36:1941–1948; 1985.
93. Schwartz, A. S.; Marchok, P. L. Depression of morphine-seeking behavior by dopamine inhibition. Nature 248:257–258; 1974.
94. Sherman, J. E.; Pickman, C.; Rice, A.; Liebeskind, J. C.; Holman, E. W. Rewarding and aversive effects of morphine: Temporal and pharmacological properties. Pharmacol. Biochem. Behav. 13:501–505; 1980.
95. Sherman, J. E.; Roberts, T.; Roskam, S. E.; Holman, E. W. Temporal properties of the rewarding and aversive effects of amphetamine in rats. Pharmacol. Biochem. Behav. 13:597–599; 1980.
96. Shippenberg, T. S.; Bals-Kubik, R.; Herz, A. Motivational properties of opioids: evidence that an activation of delta-receptors mediates reinforcement processes. Brain Res. 436:234–239; 1987.
97. Shippenberg, T. S.; Herz, A. Place preference conditioning reveals the involvement of D1-dopamine receptors in the motivational properties of mu- and kappa-opioid agonists. Brain Res. 436: 169–172; 1987.
98. Shippenberg, T. S.; Herz, A. Motivational effects of opioids: influence of D-1 versus D-2 receptor antagonists. Eur. J. Pharmacol. 151:233–242; 1988.
99. Skinner, B. F. The behavior of organisms. New York: Appleton-Century-Crofts; 1938.
100. Spyraki, C.; Fibiger, H. C. A role for the mesolimbic dopamine system in the reinforcing properties of diazepam. Psychopharmacology (Berlin) 94:133–137; 1988.
101. Spyraki, C.; Fibiger, H. C.; Phillips, A. G. Attenuation by haloperidol of place preference conditioning using food reinforcement. Psychopharmacology (Berlin) 77:379–382; 1982.
102. Spyraki, C.; Fibiger, H. C.; Phillips, A. G. Dopaminergic substrate of amphetamine-induced place preference conditioning. Brain Res. 253:185–193; 1982.
103. Spyraki, C.; Fibiger, H. C.; Phillips, A. G. Cocaine-induced place preference conditioning: lack of effects of neuroleptics and 6-hydroxydopamine lesions. Brain Res. 253:195–203; 1982.
104. Spyraki, C.; Fibiger, H. C.; Phillips, A. G. Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system. Psychopharmacology (Berlin) 79:278–283; 1983.
105. Spyraki, C.; Kazandjian, A.; Varonos, D. Diazepam-induced place preference conditioning: appetitive and antiaversive properties. Psychopharmacology (Berlin) 87:225–232; 1985.
106. Spyraki, C.; Nomikos, G. G.; Galanopoulou, P.; Daifotis, Z. Drug-induced place preference in rats with 5,7-dihydroxytryptamine lesions of the nucleus accumbens. Behav. Brain Res. 29:127–134; 1988.
107. Spyraki, C.; Nomikos, G. G.; Varonos, D. D. Intravenous cocaine-induced place preference: attenuation by haloperidol. Behav. Brain Res. 26:57–62; 1987.
108. Stapleton, J. M.; Lind, M. D.; Merriman, V. J.; Bozarth, M. A.; Reid, L. D. Affective consequences and subsequent effects on morphine self-administration of d-ala$^2$-methionine enkephalin. Physiol. Psychol. 7:146–152; 1979.
109. Swerdlow, N. R.; Swanson, L. W.; Koob, G. F. Electrolytic lesions of the substantia innominata and lateral preoptic area attenuate the 'supersensitive' locomotor response to apomorphine resulting from denervation of the nucleus accumbens. Brain Res. 306:141–148; 1984.
110. Swerdlow, N. R.; Koob, G. F. Restrained rats learn amphetamine-conditioned locomotion, but not place preference. Psychopharmacology (Berlin) 84:163–166; 1984.
111. Tombaugh, T. N.; Grandmaison, L. J.; Zito, K. A. Establishment of secondary reinforcement in sign tracking and place preference tests following pimozide treatment. Pharmacol. Biochem. Behav. 17: 665–670; 1982.
112. Ungerstedt, U. Central dopamine mechanisms and unconditioned behavior. In: Horn, A. S.; Hokfelt, J.; Westerink, B. H. C., eds. The neurobiology of dopamine. London: Academic Press; 1979:577–596.
113. van der Kooy, D.; Mucha, R. F.; O'Shaughnessy, M.; Bucenieks, P. Reinforcing effects of brain microinjections of morphine revealed by conditioned place preference. Brain Res. 243:107–117; 1982.
114. van der Kooy, D.; Swerdlow, N. R.; Koob, G. F. Paradoxical reinforcing properties of apomorphine: effects of nucleus accumbens and area postrema lesions. Brain Res. 259:111–118; 1983.
115. Vezina, P.; Stewart, J. Conditioned locomotion and place preference elicited by tactile cues paired exclusively with morphine in an open field. Psychopharmacology (Berlin) 91:375–380; 1987.
116. Vezina, P.; Stewart, J. Morphine conditioned place preference and locomotion: the effect of confinement during training. Psychopharmacology (Berlin) 93:257–260; 1987.
117. White, N. M.; Carr, G. D. The conditioned place preference is affected by two independent reinforcement processes. Pharmacol. Biochem. Behav. 23:37–42; 1985.
118. Wise, R. A. Neuroleptics and operant behavior: The anhedonia hypothesis. Behav. Brain Sci. 5:39–87; 1982.
119. Wise, R. A. The brain and reward. In: Liebeman, J. M.; Cooper, S. J., eds. The neuropharmacological basis of reward. New York: Oxford University Press; 1989:377–424.
120. Wise, R. A.; Bozarth, M. A. A psychomotor theory of addiction. Psychol. Rev. 94(3):469–492; 1987.
121. Zito, K. A.; Bechara, A.; Greenwood, C.; van der Kooy, D. The dopamine innervation of the visceral cortex mediates the aversive effects of opiates. Pharmacol. Biochem. Behav. 30:693–699; 1988.