

MINI-SYMPOSIUM

IV. DISCRIMINATIVE STIMULUS EFFECTS OF NARCOTICS:  
EVIDENCE FOR MULTIPLE RECEPTOR-MEDIATED ACTIONS

Seymore Herling and James H. Woods

Departments of Pharmacology and Psychology  
University of Michigan  
Ann Arbor, Michigan 48109

The different pharmacological syndromes produced by morphine and related drugs in the chronic spinal dog led Martin and his colleagues (1,2) to suggest that these drugs exert their agonist actions by interacting with three distinct receptors ( $\mu$ ,  $\kappa$ , and  $\sigma$ ). Morphine was hypothesized to be an agonist for the  $\mu$  receptor, ketazocine (ketocyclazocine) was an agonist for the  $\kappa$  receptor, and SKF-10,047 was an agonist for the  $\sigma$  receptor. The effects of these three drugs in the chronic spinal dog were reversed by the narcotic antagonist, naltrexone, indicating that the effects of these drugs are narcotic agonist effects (1).

In addition to the different effects of these narcotics in the non-dependent chronic spinal dog, the effects of morphine, ketazocine, and SKF-10,047 in several other behavioral and physiological preparations are consistent with the concept of multiple receptors. For example, while ketazocine and ethylketazocine, like morphine, produce analgesia, these compounds, unlike morphine, do not suppress signs of narcotic abstinence in the morphine-dependent rhesus monkey or morphine-dependent chronic spinal dog (1-5). Further, the characteristics of ketazocine withdrawal and antagonist-precipitated abstinence syndromes, although similar to those of cyclazocine, are qualitatively different from those of morphine (1,2). In rhesus monkeys, ketazocine, ethylketazocine, and SKF-10,047 maintain lever pressing at rates comparable to or below those maintained by saline, and well below response rates maintained by codeine or morphine (5,6), suggesting that the former set of drugs have limited reinforcing effect.

In recent years, there have been numerous studies on the discriminative stimulus properties of morphine and related narcotic analgesics in a variety of animal species (7-12). Rats, for example, can be trained to reliably emit one response following an injection of drug and an alternate response following a saline injection. Often, when administered other drugs, only those compounds that share the training drug's other pharmacologic actions will produce the training drug response (7,13-15). Several investigators have suggested that the discriminative stimulus effects of narcotic analgesics in animals are analogous to the subjective effects of the drugs in man (7,8,13): Rats trained to discriminate morphine from saline, for example, usually generalize only to other opioid analgesics that produce morphine-like subjective effects (7,14,15).

The discriminative effect produced by morphine has several characteristics which distinguish it: it is antagonized by naloxone or naltrexone, it is stereospecific, and it is pharmacologically specific to the extent that a variety of narcotic analgesics such as fentanyl, heroin, and levorphanol

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produce discriminative effects similar to those of morphine, while drugs such as d-amphetamine, pentobarbital, ketamine, chlorpromazine, and  $\Delta^9$ THC do not (9,14-16). Moreover, it has become increasingly evident that differences in the discriminative effects among narcotics exist (17,18).

The present paper reviews recent studies that have utilized drug discrimination techniques to analyze the actions of narcotic analgesics and related compounds and relates these findings to the hypothesis of Martin and his colleagues that multiple receptors mediate the effects of narcotics<sup>1</sup>. In addition, although the rat has been the most extensively used animal species for studying the discriminative stimulus properties of drugs, more recently, studies using squirrel monkeys (9,10), rhesus monkeys (12,19-21), and pigeons (11,16) have been conducted, thus making it possible to evaluate the species generality of multiple receptor models of narcotic action.

#### Discriminative stimulus effects of morphine-like ( $\mu$ receptor) agonists

**Rat.** Morphine can serve as a discriminative stimulus in the rat in a variety of tasks (22-27). Many narcotics, when administered to rats trained to discriminate morphine from saline, produce morphine-appropriate responses. These include fentanyl, methadone, meperidine, heroin, codeine, oxymorphone, levorphanol, propofol, etonitazene, phenazocine, propoxyphene, and butorphanol (14,15,23,28-31). Fentanyl, a potent narcotic analgesic that shares many, if not all, of the pharmacologic actions of morphine, including its discriminative effects, has also been used as a training stimulus in rats. Although extensive comparisons are lacking, narcotics that produce morphine-appropriate responding also produce fentanyl-appropriate responses (30,32-35). Many compounds that produce morphine- or fentanyl-appropriate responding in rats produce morphine-like subjective effects in man (37).

Not all narcotic analgesics produce discriminative stimulus effects like those of morphine or fentanyl. Ketazocine, a prototypic  $\kappa$  receptor agonist, does not produce morphine-appropriate responses (15,36). Similarly, the mixed agonist-antagonist, nalorphine, fails to produce discriminative effects similar to those of either morphine (15) or fentanyl (17). Cyclazocine, another narcotic with mixed agonist-antagonist activity, does not consistently produce morphine-like discriminative effects in rats (14,31). In man, cyclazocine and other analgesics with activity as morphine antagonists (e.g., nalorphine) produce non-morphine-like subjective effects ranging from tiredness and drunkenness to disorientation and psychotomimetic symptoms (38,40). Some drugs with antagonist activity (e.g., pentazocine, nalbuphine) exhibit both morphine-like and cyclazocine-like agonist properties.

Although narcotics with mixed agonist-antagonist activity (e.g., nalorphine, nalbuphine, oxilorphan, cyclazocine, SKF-10,047) and pure narcotic antagonists (e.g., naloxone) generally fail to produce morphine- or fentanyl-like discriminative effects (15,29-31,36), exceptions to this generalization exist. Cyclazocine, which fails to produce discriminative effects similar to those of morphine (14,31), generalizes to fentanyl (17), and pentazocine, which produces morphine-appropriate responding under some conditions (14,31), is not entirely morphine-like in others (29). In postaddict

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<sup>1</sup>The term narcotic is used in this paper to refer to compounds that share, in a variety of systems, agonist actions with drugs (e.g., morphine) that are thought to produce these effects through narcotic receptors or to compounds that block these actions (i.e., narcotic antagonists).

human volunteers, low doses of cyclazocine are morphine-like, while higher doses produce psychotomimetic and sedative effects (37). Similarly, pentazocine exhibits a mixture of agonist properties which resemble those of both morphine and nalorphine (37). Thus, it should not be surprising that the discriminative stimulus effects of cyclazocine, pentazocine, and other narcotics with mixed agonist-antagonist activity might differ across experimental conditions. Recently, Shannon and Holtzman (31) have shown that differences in the training dose of morphine can alter the ability of several drugs to produce morphine-appropriate responses. The relative discriminability of morphine and fentanyl, at the doses used to assess the discriminative effects of mixed agonist-antagonists, might differ both quantitatively and qualitatively across experimental conditions, resulting in differences in experimental results. Nevertheless, there are sufficient examples of narcotics that fail to produce morphine-appropriate responding in rats [e.g., nalorphine, oxilorphan, SKF-10,047 (15,29,36)] to suggest that these drugs may possess agonist actions different from those of morphine. The characteristics of the discriminative effects of some of these compounds will be examined below. Before discussing the effects of these drugs, however, the discriminative stimulus effects of morphine-like agonists in species other than the rat will be reviewed.

Squirrel monkey. Many narcotics that produce morphine-appropriate responding in rats also produce morphine-appropriate responding in squirrel monkeys (Table I). A number of narcotic antagonists, however, that completely substitute for morphine in rats [e.g., pentazocine, butorphanol (14,15)] fail to produce morphine-appropriate responding in squirrel monkeys (9,18). Holtzman et al. (18) suggest that these differences may either reflect true differences in the response of these two species to narcotic antagonists or that differences in the effects of mixed narcotic agonist-antagonists may be due to the relative magnitude of the training doses of morphine used in the two species. For example, nalbuphine generalizes to a low training dose of morphine [1.75 mg/kg (31)] in the rat, but fails to substitute completely for higher training doses [3.0-5.6 mg/kg (15,31)]. Similarly, pentazocine has been shown to generalize to low or moderate doses of morphine [1.75-5.6 mg/kg (14, 31)], but not completely to a higher training dose [7.5 mg/kg (29)]. Nevertheless, a number of narcotic mixed agonist-antagonists (e.g., cyclazocine, levallorphan, oxilorphan) and a prototypic  $\kappa$  agonist, ketazocine, fail to produce morphine-like discriminative effects in both the rat and the squirrel monkey (15,18,31, Holtzman and Schaefer, unpublished observations), suggesting further that these narcotics might possess discriminative stimulus effects that are different from those of morphine in these species. In this respect, the squirrel monkey may be more selective as to which narcotics with morphine antagonist activity have discriminative effects similar to those of morphine.

Rhesus monkey. To date, no studies on the discriminative stimulus effects of morphine in rhesus monkeys have been reported. The morphine-like narcotics codeine and etorphine, however, have been used as discriminative stimuli in this species (12,19,21). The results of these studies are summarized in Table I, and, where comparisons can be made, drugs that produce etorphine- or codeine-appropriate responding in rhesus monkeys are similar to those that produce morphine-appropriate responding in the squirrel monkey. As with squirrel monkeys, a number of narcotics with mixed agonist-antagonist activity (e.g., cyclazocine, pentazocine) fail to produce morphine-like discriminative effects in rhesus monkeys. Ethylketazocine, a narcotic analgesic devoid of any narcotic antagonist activity (39), also fails to produce a codeine- or etorphine-like discriminative effect in the rhesus monkey, as does the mixed agonist-antagonist, SKF-10,047. The inability of a prototypic  $\kappa$  receptor agonist, ethylketazocine, and the  $\sigma$  receptor agonist, SKF-10,047, to produce  $\mu$ -like discriminative effects (Table I) lends support to the hypothesis that multiple receptors mediate the actions of narcotics.

TABLE I

Drugs that Generalize to or Fail to Generalize to Morphine-like Agonists in the Squirrel Monkey and Rhesus Monkey

Training drug (dose)	Squirrel monkey	Rhesus monkey	
	Morphine (3.0 mg/kg)	Etorphine (0.001 mg/kg)	Codeine (3.2 mg/kg)
Narcotics that generalize:	Fentanyl (9) Oxymorphone (9) Levorphanol (9) Methadone (9) Meperidine (9)	Morphine (19) Codeine (19) Meperidine (19)	Morphine (21) Etorphine (21) Levorphanol (21) Fentanyl (21)
Narcotics that fail to generalize:	Cyclazocine (18) Pentazocine (18) Levallorphan <sup>1</sup> Oxilorphan <sup>1</sup> Ketazocine <sup>1</sup> Butorphanol (18) Nalbuphine (18) Naloxone (9)	Pentazocine (19) SKF-10,047 (19) Ethylketazocine (19)	Cyclazocine (21) SKF-10,047 (21) Ethylketazocine (21)
Non-narcotics that fail to generalize:	Dextrorphan (9) d-Amphetamine (9) Pentobarbital (9)		Dextrorphan (21) Ketamine (21) Methohexital (21)

<sup>1</sup>Holtzman and Schaefer, unpublished observations.

**Pigeon.** Pigeons trained to discriminate morphine from saline (Table II) generalize to several drugs that would normally be classified as  $\mu$  receptor agonists (e.g., levorphanol, methadone, codeine) and a number of compounds that in other species might normally be classified as  $\kappa$  receptor agonists (e.g., ethylketazocine, ketazocine, UM 909, UM 1072). The  $\kappa$  agonists in this grouping of drugs are noted for their lack of antagonist activity (1,4,5). In contrast, cyclazocine, nalorphine, and SKF-10,047, narcotics with morphine antagonist activity (1), fail to produce morphine-appropriate responding in the pigeon. Thus, unlike either the rhesus monkey, in which ethylketazocine fails to produce morphine-like discriminative effects, or the squirrel monkey (Table I) and the rat, in which ketazocine does not substitute for morphine, there appears to be no distinction between the discriminative effects of  $\mu$  and  $\kappa$  receptor agonists in the pigeon (Table II). On the other hand, cyclazocine and SKF-10,047, narcotics that possess both morphine antagonist activity and behavioral effects resembling those of agonists acting at the proposed  $\sigma$  receptor (1), tend to have discriminative effects that differ from those of morphine in rats, squirrel monkeys, rhesus monkeys, and pigeons. A characterization of the discriminative stimulus effects of putative  $\kappa$  and  $\sigma$  receptor agonists follows below.

#### Discriminative stimulus effects of $\kappa$ receptor agonists

A number of analgesics with morphine antagonist activity (e.g., cyclazocine, nalorphine) produce prominent subjective effects in man that often include sedative and psychotomimetic effects (40,41). These effects are clearly distinguishable from the syndrome of subjective effects produced by morphine

TABLE II  
Drugs that Generalize to or Fail to Generalize to Morphine in the Pigeon

Narcotics that generalize:	Levorphanol (16)	Ethylketazocine (11)
	Methadone (16)	Ketazocine (11)
	Codeine (11)	UM 1072 <sup>2</sup> (11)
	FK 33824 <sup>1</sup> (11)	UM 909 <sup>3</sup> (11)
Narcotics that fail to generalize:	Cyclazocine (11)	Pentazocine (11)
	SKF-10,047 (11)	Meperidine (11)
	Nalorphine (11)	
Non-narcotics that fail to generalize:	Dextrorphan (11,16)	Clonidine (11)
	$\Delta^9$ -THC (16)	UM 1046 <sup>4</sup> (11)
	d-LSD (16)	Ketamine (11)
	Pentobarbital (11,16)	

<sup>1</sup>Tyr-D-Ala-Gly-MePhe-Met(O)-ol

<sup>2</sup>(±)-(1R/S, 5R/S, 9R/S, 2''R/S)-5,9-dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan

<sup>3</sup>2-(2-methyl-3-furylmethyl)-2'-hydroxy- $\alpha$ -5,9-dimethyl-6,7-benzomorphan

<sup>4</sup>3-cyclopropylmethyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6-methyl-3-benzazocine

(38,40). In the Martin et al. classification of narcotics in the chronic spinal dog (1), cyclazocine, ketazocine, and ethylketazocine are agonists at the  $\kappa$  receptor, with cyclazocine being distinguished from the latter two compounds in that it is also an agonist at the  $\sigma$  receptor and an antagonist at the  $\mu$  receptor. Cyclazocine is thus both a  $\kappa$  and a  $\sigma$  receptor agonist, while ketazocine and ethylketazocine are agonists primarily at the  $\kappa$  receptor.

**Rat.** Cyclazocine has been shown to serve as a discriminative stimulus in the rat by a number of investigators, and there has been one report of ketazocine as a discriminative stimulus (36,42-45). As noted above, rats trained to discriminate between morphine and saline generalize only partially, or not at all, to either cyclazocine or ketazocine (15,31), and conversely, rats trained to discriminate between cyclazocine and saline show little or no generalization to morphine (42-44). Under some circumstances, however, morphine does substitute for cyclazocine or ketazocine in the rat (36,45). Several procedural differences might account for these discrepancies, including the method and measure of generalization testing, the type of reinforcer, and the dose of the training drug used. For example, Teal and Holtzman (44) have shown that differences in the training dose of cyclazocine can alter the ability of a number of narcotics (e.g., ethylketazocine, pentazocine, levallorphan) to produce cyclazocine-appropriate responses.

In addition to the ability of the  $\kappa$  agonists, ketazocine and ethylketazocine, and the  $\sigma$  agonist, SKF-10,047, to produce cyclazocine-appropriate responding in rats (44,45), Teal and Holtzman (44) have also shown that the non-opioid dissociative anesthetics, phencyclidine and ketamine, are capable of producing a cyclazocine-like discriminative stimulus. Not all psychotomimetic drugs, however, produce cyclazocine-appropriate responding in rats. Mescaline, *d*-amphetamine, and LSD do not generalize to cyclazocine (42-44). In man, ketamine and phencyclidine produce dysphoric and psychotomimetic effects (46), as does cyclazocine (37,38,40), while mescaline, *d*-amphetamine, and LSD produce subjective effects that are unlike those of phencyclidine (47). The discrim-

inactive stimulus effects of cyclazocine in the rat, then, appear to include a relatively specific non-opioid (phencyclidine-like) action, and it has been proposed (44) that this effect may be analogous to the psychotomimetic effects that are known to be produced by phencyclidine and ketamine in man.

The relationship of the non-opioid (i.e., phencyclidine-like) discriminative effects of cyclazocine in the rat to the pharmacologic actions of  $\kappa$  or  $\sigma$  agonists in the dog, is unclear. Martin et al. (1) believe that  $\sigma$  receptor activation is responsible for the hallucinogenic effects of SKF-10,047 in man and delirium in the dog. Perhaps these effects of SKF-10,047 are related to the subjective effects produced by phencyclidine in man. However, while cyclazocine-induced hallucinations and dysphoria in man (48) and SKF-10,047-induced canine delirium and autonomic stimulation (1) are antagonized by naloxone or naltrexone, the cyclazocine-like discriminative stimulus effects produced by ketamine, phencyclidine, or cyclazocine in the rat are not well antagonized, if at all, by naloxone or naltrexone (44).

Squirrel monkey. Cyclazocine and a number of other narcotics with mixed agonist-antagonist activity (e.g., pentazocine, nalbuphine, levallorphan, oxilorphan, butorphanol) fail to generalize in squirrel monkeys trained to discriminate morphine from saline (Table I). Similarly, a prototypic  $\kappa$  receptor agonist, ketazocine, does not produce morphine-appropriate responding. In squirrel monkeys trained to discriminate cyclazocine from saline, however, ketazocine, the mixed narcotic agonist-antagonists, oxilorphan, levallorphan, and butorphanol, and the prototypic  $\sigma$  receptor agonist, SKF-10,047, produce cyclazocine-like discriminative effects, while morphine does not (Table III). Thus, a clear distinction can be made between morphine-like and cyclazocine-like discriminative effects in the squirrel monkey.

However, not all narcotics with mixed agonist-antagonist activity (e.g., nalorphine, pentazocine, nalbuphine) produce discriminative effects similar to those of cyclazocine, suggesting that some of these drugs (e.g., nalbuphine, pentazocine) have discriminative effects in the squirrel monkey that are unlike those of either morphine (Table I) or cyclazocine (Table III). The similarity of the discriminative stimulus effects of cyclazocine and those of ketamine or phencyclidine in the squirrel monkey has yet to be evaluated. Interestingly, the antitussives, dextrophan and dextromethorphan, produce cyclazocine-like discriminative effects in the squirrel monkey (49).

Rhesus monkey. Although cyclazocine has not been used as a discriminative stimulus in rhesus monkeys, Hein et al. (20) have studied the discriminative stimulus effects of ethylketazocine (Table III). Several drugs that produce cyclazocine-appropriate responding in squirrel monkeys were shown to produce ethylketazocine-appropriate responding in rhesus monkeys. These included: ketazocine, cyclazocine, and SKF-10,047. Moreover, a number of narcotics that have  $\mu$ -like discriminative effects in rhesus monkeys and squirrel monkeys (e.g., codeine, morphine, etorphine, levorphanol, meperidine; Table I) failed to produce ethylketazocine-appropriate responding in the rhesus monkey (20). In both the squirrel monkey and the rhesus monkey, then, and under many conditions in the rat, distinctions can be made between morphine-like ( $\mu$ ) and cyclazocine- or ethylketazocine-like ( $\kappa$ ) drugs based on the discriminative effects of these narcotics.

Pigeon. As was shown in Table II, pigeons trained to discriminate morphine from saline, generalize to several drugs that in other species might be classified as  $\kappa$  receptor agonists (e.g., ethylketazocine, ketazocine). Conversely, if pigeons are trained to discriminate between ethylketazocine and saline, several  $\mu$  receptor agonists (e.g., morphine, codeine, etorphine) produce ethylketazocine-appropriate responding (Table III). Narcotics with

TABLE III  
Drugs that Generalize to or Fail to Generalize to  $\kappa$  Agonists  
in Squirrel Monkeys, Rhesus Monkeys and Pigeons

Training drug (dose)	Squirrel monkey Cyclazocine (10,49) (0.1 mg/kg)	Rhesus monkey Ethylketazocine (20) (0.01 mg/kg)	Pigeon Ethylketazocine <sup>4</sup> (0.32 mg/kg)
<u>Drugs that generalize</u>			
Narcotics:	Ketazocine SKF-10,047 <sup>1</sup> Oxilorphan Levallorphan Butorphanol	Ketazocine SKF-10,047 Cyclazocine Cyclorphan UM 1072 <sup>5</sup> UM 909 <sup>5</sup> Nalorphine	Ketazocine Morphine Codeine Etorphine UM 1072 <sup>5</sup> UM 909 <sup>5</sup> Pentazocine
Non-narcotics:	Dextrorphan Dextromethorphan		
<u>Drugs that fail to generalize</u>			
Narcotics:	Nalorphine Morphine Pentazocine Nalbuphine Nalmexone Naloxone	Codeine Morphine Pentazocine Etorphine Levorphanol Meperidine	Nalorphine Cyclazocine SKF-10,047
Non-narcotics:	Pentobarbital Scopolamine d-Amphetamine Mescaline	Pentobarbital UM 1071-S <sup>2</sup> d-Ethylketazocine Ketamine <sup>3</sup> Dextrorphan Apomorphine Quaternary nalorphine Phencyclidine <sup>3</sup>	Pentobarbital UM 1071-S <sup>2</sup> d-Ethylketazocine Ketamine Dextrorphan Apomorphine

<sup>1</sup>Holtzman, unpublished observations

<sup>2</sup>(+)-(1S, 5S, 9S, 2''S)-5,9-dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan

<sup>3</sup>Ketamine and phencyclidine produced ethylketazocine-appropriate responding in 50% of the rhesus monkeys tested

<sup>4</sup>Hein, unpublished observations

<sup>5</sup>See Table II for chemical formulae

activity as morphine antagonists, however, most notably cyclazocine, SKF-10,047, and nalorphine, fail to produce either morphine- or ethylketazocine-appropriate responding in the pigeon. Thus, differences in the discriminative effects of narcotics in the pigeon are unique compared to the effects of these drugs in other species in which narcotic discriminations have been studied. In the pigeon, morphine, ethylketazocine, and ketazocine appear to share discriminative effects which are not shared by cyclazocine or SKF-10,047. In contrast, in rhesus monkeys, squirrel monkeys, and rats, the discriminative stimulus effects of morphine generally differ from those of a grouping of

drugs that includes cyclazocine, SKF-10,047, ethylketazocine, and ketazocine.

Antagonism of the discriminative stimulus effects of narcotics. Additional evidence that narcotics have actions at more than one receptor comes from studies on the antagonism of various narcotic agonists by narcotic antagonists. Naloxone, naltrexone, and diprenorphine, for example, are potent narcotic antagonists that precipitate severe abstinence syndromes in morphine-dependent dogs (50). They are, however, 20 to 60 times less potent in precipitating abstinence in cyclazocine-dependent dogs (2). Similarly, larger doses of naloxone or naltrexone are generally required to block single dose effects of nalorphine-like drugs or  $\kappa$  agonists than are needed to antagonize morphine (48,51,52,54). In drug discrimination studies, as well, differences exist in the ability of naloxone or naltrexone to antagonize the discriminative stimulus effects of different narcotics.

The discriminative effects of the  $\mu$  receptor agonists, morphine and etorphine, are effectively antagonized by low doses of naloxone or naltrexone (0.03-0.1 mg/kg) in rats, squirrel monkeys, rhesus monkeys, and pigeons (9,14, 16,36,53). In contrast, the discriminative effects of cyclazocine are completely blocked in squirrel monkeys only by a dose of naloxone that is 30 times larger than that needed to antagonize morphine in this species (9,10). Moreover, the discriminative effects of cyclazocine in rats or pigeons are not completely reversed by 10-30 mg/kg naltrexone or by 48 mg/kg naloxone (42-44, unpublished observations). Although less data are available on antagonism of the prototypic  $\kappa$  and  $\sigma$  agonists, ketazocine and SKF-10,047, the discriminative effects of ketazocine appear to be more readily antagonized by naloxone than are the effects of SKF-10,047 (36).

That morphine and the  $\kappa$  agonist, ethylketazocine, produce discriminative effects in the pigeon through similar mechanisms is suggested not only by the fact that the same drugs produce both morphine-appropriate (Table II) and ethylketazocine-appropriate (Table III) responding, but also by the findings that the discriminative effects of morphine and ethylketazocine are blocked by comparable doses of naltrexone in this species (11,53, unpublished observations). In contrast, the discriminative stimulus produced by ethylketazocine in the rhesus monkey is not reversed by naltrexone in all animals (20).

The inability of narcotic antagonists to block the discriminative effects of some narcotic analgesics suggests that non-opioid actions may be responsible for at least part of the discriminative effects of these drugs. Moreover, since differences among species exist in the ability of naloxone or naltrexone to reverse the discriminative effects of various narcotics, some drugs may be more or less "narcotic" in their discriminative effects depending on the species used to assess these effects.

#### Discriminative stimulus effects of $\sigma$ receptor agonists

The classification of SKF-10,047 and cyclazocine as narcotic  $\sigma$  agonists relies on the findings by Martin and others that the effects of these drugs are blocked by naloxone and naltrexone. For example, cyclazocine produces hallucinations and dysphoric effects in man that are reversed by naloxone (48). Similarly, SKF-10,047- and cyclazocine-induced canine delirium and autonomic stimulation are antagonized by naloxone and naltrexone (1,2). In squirrel monkeys trained to discriminate cyclazocine from saline, the discriminative effects of cyclazocine are blocked by naloxone; in rats, however, the discriminative effects of cyclazocine are not completely blocked by doses of naloxone or naltrexone as high as 30 or 48 mg/kg, respectively. These inter-species differences may indicate that the effects of cyclazocine in the rat include a relatively more important non-opiate component as



compared to the effects of cyclazocine in the squirrel monkey or in man.

Rat. As noted above, rats trained to discriminate cyclazocine from saline, generalize to the non-opioids, ketamine and phencyclidine, and to the prototypic  $\sigma$  receptor agonist, SKF-10,047 (44). Similarly, if rats are trained to discriminate between phencyclidine and saline, both cyclazocine and SKF-10,047 produce phencyclidine-appropriate responding (Table IV). Although the  $\kappa$  receptor agonists, ketazocine and ethylketazocine, produce cyclazocine-appropriate responding in the rat (44), neither compound generalizes to phencyclidine (Table IV). These results indicate that cyclazocine and SKF-10,047 have actions in common with both  $\kappa$  agonists and with phencyclidine-like drugs, but that ketazocine and phencyclidine have distinguishable discriminative stimulus effects. Thus, in the rat, the  $\kappa$  agonist activity of cyclazocine and SKF-10,047 might best be represented by the discriminative effects of ketazocine or ethylketazocine, while some additional non-narcotic action is best represented by their phencyclidine-like activity. The cyclazocine-like actions of phencyclidine are not antagonized by naloxone (44).

In man, phencyclidine produces sensory disturbances and psychotomimetic effects that are unique compared to the subjective effects produced by other psychotropic drugs (47,55-57). SKF-10,047 also has psychotomimetic activity in man (58), as does cyclazocine (37,38,40). In the chronic spinal dog, phencyclidine shares effects with SKF-10,047 and cyclazocine (1,2,59) that are not produced by other classes of psychoactive drugs (59).

In drug discrimination experiments, as well, rats trained to discriminate between saline and phencyclidine generalize to ketamine, but not to drugs from other pharmacological classes such as LSD, quipazine, apomorphine,  $\Delta^9$ -THC, d-amphetamine, atropine, diazepam, pentobarbital, and morphine (60-62,64), indicating a pharmacologically specific action. In addition, since cyclazocine, SKF-10,047, and dextrophan produce phencyclidine-appropriate responding, while the structurally related compounds ketazocine, pentazocine, and dextromethorphan do not (63), critical structural requirements appear necessary to produce a phencyclidine-like discriminative stimulus. These findings suggest that the discriminative effects of phencyclidine may be mediated at specific neuronal sites and are not simply the result of nonselective action (63).

Yet, as noted above, the relationship of the phencyclidine-like actions of narcotics to the postulated  $\sigma$  receptor is not entirely clear. The hallucinogenic effects of some narcotics in man and delirium in dog are thought to be mediated by the  $\sigma$  receptor for which SKF-10,047 and cyclazocine are prototypic agonists (1). While these effects are antagonized by naloxone or naltrexone (1,2), the phencyclidine-like discriminative effects engendered by cyclazocine in the rat are not (63). Since appropriate concentrations of SKF-10,047 displace  $^3\text{H}$ -phencyclidine binding in rat brain membranes, while naloxone, ketazocine, morphine, and etorphine do not (65,66), Holtzman (63) has proposed that some opioids (e.g., cyclazocine, SKF-10,047) produce discriminative effects through interactions with neuronal substrates that mediate the effects of phencyclidine rather than through interactions with opiate receptors.

Squirrel monkey and rhesus monkey. Recently, the discriminative stimulus effects of phencyclidine and the related congener, ketamine, have been studied in monkeys (Table IV). As was shown for the rat, squirrel monkeys trained to discriminate phencyclidine from saline generalize to ketamine and several other cyclohexylamines, as well as to dexoxadrol and etoxadrol. In man, dexoxadrol is an analgesic which produces a high degree of psychotomimetic activity (67). In addition, appropriate doses of dexoxadrol produce a euphoria in man which is more akin to that seen following barbiturates than



that produced by morphine (68).

In rhesus monkeys, dexoxadrol generalizes to ketamine, as does dextrorphan (Table IV). Furthermore, while dexoxadrol and dextrorphan engender discriminative effects similar to those of ketamine, their respective levo-isomers, levoadrol and levorphanol, do not, indicating a stereospecific requirement for the ketamine discriminative effect.

In contrast to the rat, in which both cyclazocine and SKF-10,047 produce phencyclidine-appropriate responding (63), preliminary findings indicate that neither compound produces discriminative effects similar to those of ketamine in the rhesus monkey (Table IV). However, when the stereoisomers of SKF-10,047 were studied, the dextro-isomer, but not the levo-isomer, was found to produce ketamine-appropriate responding (unpublished observations). As noted earlier, cyclazocine and SKF-10,047 produce discriminative effects in rhesus monkeys similar to those of the  $\kappa$  agonist, ethylketazocine (20). Whether the ethylketazocine-like actions of cyclazocine and SKF-10,047 reside in the levo- or dextro-isomers of these compounds remains to be determined.

Pigeon. Several similarities exist between the discriminative effects of ketamine in the pigeon and the discriminative effects of phencyclidine in the rat. First, the discriminative effects of the two drugs are essentially interchangeable. Secondly, just as cyclazocine, SKF-10,047, and dextrorphan engender phencyclidine-appropriate responding in the rat (63), each of these drugs produces ketamine-appropriate responding in the pigeon (Table IV). Moreover, a number of drugs that fail to produce phencyclidine-appropriate responding in the rat (e.g., morphine, pentazocine, ethylketazocine) also fail to produce ketamine responses in the pigeon. Thus, in several species, the discriminative effects of some of these compounds (e.g., cyclazocine, SKF-10,047, dextrorphan) are more like those produced by phencyclidine and ketamine than they are like those engendered by  $\mu$  agonists (e.g., morphine) or  $\kappa$  agonists (e.g., ketazocine, ethylketazocine). Also, since the discriminative stimulus effects of phencyclidine-like opioids are generally resistant to blockade by narcotic antagonists, it may be that the discriminative effects of these drugs are mediated by receptors other than those that subserve the effects of narcotics.

#### Summary

Results of studies on the discriminative stimulus effects of narcotics are consistent with the hypothesis that multiple receptors mediate the effects of these compounds. In the rat, at least three subsets of discriminative effects exist, although some drugs appear to have effects that transcend more than one subset. The discriminative effects of morphine-like narcotics ( $\mu$  agonists), for example, are often clearly distinguishable from the discriminative effects produced by  $\kappa$  agonists, such as ketazocine, and from those produced by phencyclidine-like agonists, such as SKF-10,047 and cyclazocine. Cyclazocine, however, has been reported to have discriminative effects in common with morphine (45) and fentanyl (17) and appears to have  $\kappa$ -like, in addition to phencyclidine-like, discriminative effects. The relative ability of pure narcotic antagonists to block the discriminative effects of these compounds also provides evidence for distinct pharmacologic actions of these drugs. In the rat, the discriminative effects of morphine are blocked by doses of naloxone that are considerably smaller than those that are needed to block the discriminative effects of cyclazocine (44). The discriminative effects of phencyclidine are not altered at all by naltrexone (63).

In the squirrel monkey and rhesus monkey, there also appear to be at least three distinct subsets of discriminative stimulus effects. These are represented by  $\mu$  agonists (e.g., morphine),  $\kappa$  agonists (e.g., ketazocine,

ethylketazocine, cyclazocine, SKF-10,047) and phencyclidine-like agonists (e.g., dextrorphan, dexoxadrol). The discriminative effects of morphine and etorphine in monkeys are blocked by relatively small doses of naloxone or naltrexone. The discriminative effects of  $\kappa$  agonists (e.g., cyclazocine, ethylketazocine), on the other hand, appear to be less sensitive to antagonist blockade. Preliminary observations on the discriminative stimulus effects of phencyclidine-like compounds in the rhesus monkey suggest that these effects are totally resistant to antagonism by naltrexone.

Finally, in contrast to the effects of these drugs in the mammalian species that have been studied, the discriminative stimulus effects of narcotics in the pigeon appear to fall into only two subsets. One subset includes both  $\mu$  agonists (e.g., morphine) and  $\kappa$  agonists (e.g., ketazocine, ethylketazocine). The discriminative effects of these drugs are readily blocked by small doses of naltrexone. The second subset of compounds in the pigeon includes drugs that produce phencyclidine-like discriminative effects (e.g., cyclazocine, SKF-10,047). The discriminative effects of these drugs are not antagonized by naltrexone.

Differences in the response of various species to the effects of narcotics have important implications for receptor theories of narcotic action. For example, the finding that pigeons, in contrast to primates and rats, do not distinguish between  $\mu$  agonists (e.g., morphine) and  $\kappa$  agonists (e.g., ethylketazocine), suggests that the pigeon may lack biological substrates necessary for such distinctions. In addition, the finding that in some species certain compounds (e.g., dextrorphan, SKF-10,047, cyclazocine) share with phencyclidine discriminative effects that are not produced by various other narcotics (e.g., morphine, codeine, ketazocine, ethylketazocine, pentazocine), may be indicative of a non-narcotic receptor-mediated action.

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