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BEHAVIORAL CHARACTERIZATION OF OPIOID MIXED AGONIST-ANTAGONISTS

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SUMMARY

The effects of agonists and partial agonists of both mu and kappa receptor systems are described in several behavioral tests in rhesus monkeys. Procedures measuring drug discrimination, drug self-administration, drug dependence, and drug-induced analgesia are differentially sensitive to the agonist and antagonist effects of various opioids. The sensitivity of each of the procedures may be modified by altering behavioral parameters or dose of drug used to establish the behavioral effect.

Key words: Opioids — Self-administration — Drug-discrimination — Physiological dependence — Analgesia — Rhesus monkey

INTRODUCTION

'The term agonist-antagonist as applied to opioid analgesics and their central nervous system actions has thus come to involve two concepts: 1) the concept of multiple receptors; 2) the concept of partial agonists' [1]. This description of the basic attributes of opioid agonist-antagonists, also referred to as partial agonists or mixed agonist-antagonists, hints at the complex nature of these drugs and the difficulties involved in classifying them and interpreting their actions. It must be determined through which of the multiple opioid receptors any given drug exerts agonist effects. In addition, the nature of its partial agonist properties, on this same or another receptor, must be described. The emphasis of the present paper is on the various procedures that have yielded information about agonist and partial agonist actions of opioids in the rhesus monkey. It seems clear that procedures that do an excellent job of indicating the receptor system on which a drug acts in the monkey do not necessarily yield concomitant information about the nature of the partial agonist effects of opioids.

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Martin [2] proposed different types of opiate receptors based on differential, naloxone-sensitive actions of specific opioids in several preparations. Since that time, and with elaborations by Martin et al. [3] in the spinal dog, the distinct opiate actions mediated by two of these receptors, the mu receptor with morphine as the prototype and the kappa receptor with ketocyclazocine as the prototype, have been well documented in a number of behavioral systems.

The rhesus monkey has been an especially useful species to differentiate mu and kappa opiates. The measures of opioid actions in this species have included analgesia, discriminative stimulus effects, fluid balance, reinforcing effects, tolerance and dependence. Each of these measures, with the exception of analgesia, in which both mu and kappa agonists are active, demonstrate the distinctive effects of mu and kappa opioids in the monkey. Even with analgesia, pA2 studies in the monkey indicate this effect may be mediated through two different receptors, mu and kappa [4].

PROCEDURES

Drug discrimination

Tests of discriminative stimulus effects have been particularly useful in differentiating mu and kappa opioids in the rhesus monkey. In this type of preparation, monkeys are trained to respond differentially (i.e. on one of two levers) depending on whether they have received an injection of a particular drug or an injection of vehicle. Monkeys trained to indicate administration of a mu agonist such as codeine will respond on the codeine-appropriate lever following administration of active doses of other mu agonists. Likewise, monkeys trained to respond on one of two levers following administration of a kappa agonist such as EKC, will respond on this lever following administration of other kappa agonists. Figure 1a shows the effects of alfentanil and EKC in three rhesus monkeys trained to discriminate the effects of 1.0 mg/kg codeine. Alfentanil produced codeine-like discriminative stimulus effects in these monkeys, whereas EKC did not. In contrast, as shown in Fig. 1b, the kappa agonist U-50488 had discriminative stimulus effects in common with EKC in three monkeys trained to indicate the interoceptive effects of 0.0032 mg/kg EKC, whereas alfentanil did not. The generality of this finding is indicated by the fact that mu agonists such as morphine, etorphine, *l*-alphaacetylmethadol (LAAM), and methadone have each been shown to produce codeine-, but not EKC-like discriminative stimulus effects in the monkey [5] whereas kappa agonists such as ketazocine, tifluadom, bremazocine, and MR2033, (+)-(1 R/S, 5 R/S, 2″ R/S)-5,9-dimethyl-2′-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan HCl) produced EKC-like but not codeine-like discriminative stimulus effects [4–6].

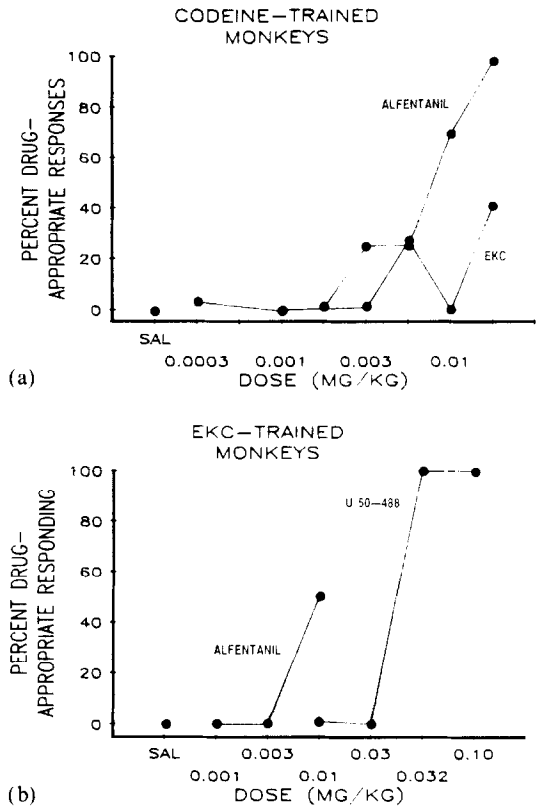

Fig. 1. Discriminative stimulus effects of alfentanil and EKC in monkeys trained to discriminate 1.0 mg/kg codeine from saline (a) and of alfentanil and U-50488 in monkeys trained to discriminate 0.0032 mg/kg EKC (b). Abscissae: dose of test drugs in mg/kg. Ordinates: percent of the total responses made on the codeine- (a) or EKC- (b) appropriate levers.

A number of mixed agonist-antagonists have been evaluated in rhesus monkeys trained to discriminate either the mu agonist etorphine (0.00032 mg/kg) or the kappa agonist EKC (0.0032 mg/kg). Nalorphine and *l*-cyclazocine produced 100% EKC-appropriate responding in all tested monkeys [5]. The agonist-antagonists buprenorphine, butorphanol, *d*-profadol, propiram, and nalbuphine did not produce discriminative effects in common with EKC; all produced more than 90% responding on the etorphine-appropriate lever indicating mu-like discriminative effects [7].

Drug self-administration

The difference in reinforcing effects of mu and kappa opioids is indicated in Fig. 2 by comparing a mu agonist, alfentanil, with a kappa agonist, U-50488, on measures of rate of responding maintained by intravenous presentation of these drugs to rhesus monkeys. Under the conditions of these experiments, monkeys were given access to 0.32 mg/kg per injection codeine

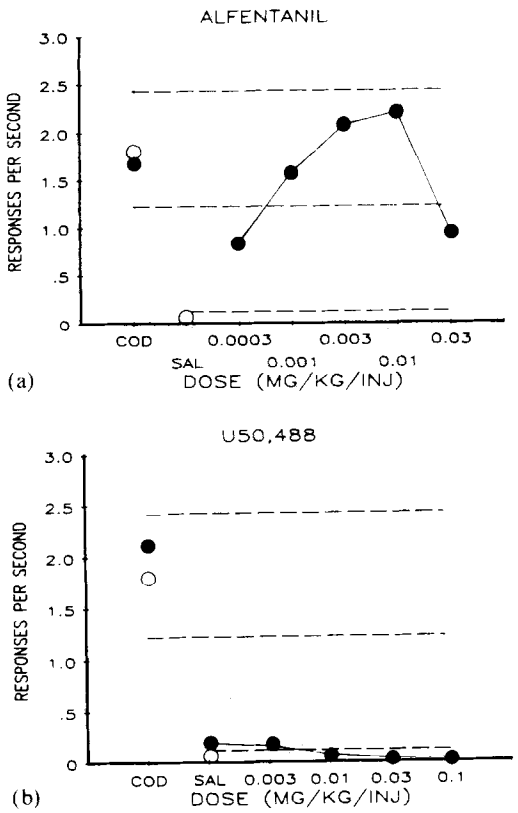

Fig. 2. Reinforcing effects of alfentanil (a) and U-50488 (b) in monkeys experienced with self-administration of 0.32 mg/kg per inj. codeine. The open circles indicate the average rate of codeine (COD)- or saline (SAL)- reinforced responding in a group of 20 monkeys. The two topmost dashed lines are +3 S.E.M. of this codeine average, and the bottommost dashed line is +3 S.E.M. of this saline average. Closed circles represent average codeine, saline and alfentanil- or U-50588-reinforced responding in three monkeys tested with these drugs. Each monkey was tested twice at each indicated dose. Abscissae: dose of alfentanil (a) or U-50488 (b), in mg/kg per inj., used to evaluate the reinforcing effects of these drugs. Ordinates: responses per second.

during two daily 130-min sessions. This dose of codeine was delivered consequent to 30 responses by the monkey on an available lever, and each drug delivery was followed by a signalled 10-min time-out period when responding had no consequence. When rates of codeine-maintained responding were stable and above 1 response/s, substitutions of the indicated doses of alfentanil, U-50488, or saline were made every third session. Each monkey received each dose on two occasions. The data points shown indicate the mean rates of responding in at least three monkeys. Rates of responding maintained by alfentanil reached more than 2 responses/s at the maximal rate-maintaining dose of 0.01 mg/kg per inj. Rates of responding maintained by U-50488, however, were never higher and were frequently lower

than rates maintained by saline. These differential reinforcing effects of mu and kappa agonists have been demonstrated with a wide variety of compounds, including the mu agonists, morphine, codeine, methadone, and heroin, and the kappa agonists, EKC, ketocyclazocine, and bremazocine. A few exceptions exist, related to the onset and duration of action of the drugs in question. LAAM, for example, is a long-acting, mu opioid that does not maintain drug self-administration in rhesus monkeys (Bertalmio, unpublished observations).

That the reinforcing effects are mediated by opioid receptors is suggested by the fact that a surmountable antagonism of the reinforcing effects of alfentanil may be obtained with the opioid antagonist quadazocine. The pA2 for quadazocine as an antagonist of the reinforcing effects of alfentanil closely approximates the pA2 obtained with the discriminative stimulus effect of this drug and other mu agonists [8].

A number of mixed agonist-antagonists have been tested for their reinforcing effects in the procedure described above. The reinforcing effects of buprenorphine, butorphanol, nalbuphine, pentazocine and picenadol have been investigated in the rhesus monkey. Each of these drugs has been shown to maintain intravenous self-administration, but at rates below those maintained by codeine [7]. Thus, with this behavioral effect, these compounds appear to share actions with mu rather than kappa opioids. The fact that they are not as efficacious as codeine suggests that they may be partial agonists in this system. However, further evaluation of the reinforcing effects must be undertaken to determine whether effects less than those produced by codeine indicate partial agonist effects or can be explained by some other mechanisms. Morphine, which is a full agonist in most other systems, does not maintain rates of responding as high as those maintained by codeine, which raises the possibility that there may be inherent differences among these drugs that serve to modulate the expression of their reinforcing effects in this paradigm. It will be necessary to modify the procedures so that drugs known to have full agonist effects produce similar, high rates of reinforced responding. It may be then possible to determine more precisely whether the mixed agonist-antagonists tested yield data indicating full or partial agonist effects.

Neither nalorphine, oxilorphan nor levallorphan maintained intravenous self-administration in the monkey [7], and there are some data from our laboratory and others [9] that nalorphine may have aversive effects. Likewise, *l*-cyclazocine did not maintain drug self-administration, although *d*-cyclazocine, with considerable phencyclidine-like activity in the monkey, showed a very modest amount of reinforcing activity [10].

Urination

The capacity of kappa, but not mu opioids, to produce increases in urine output has been demonstrated in rodents [11]. A similar finding has been reported in rhesus monkeys with bremazocine, EKC, MR 2033, tifluadom

and U-50488 [4]. Few mixed agonist-antagonists have been evaluated in tests of urine output in the rhesus monkey, so the capacity of this test to indicate partial agonist actions has not yet been determined.

Physiological dependence

Morphine-dependent monkeys deprived of morphine demonstrate characteristic withdrawal signs that are quite different from those shown by monkeys made dependent on the selective kappa agonist U-50488 and deprived of this opiate. Table I lists the various withdrawal signs associated with termination of chronic morphine or chronic U-50488 administration. Signs of morphine withdrawal are not attenuated by administration of kappa opiates such as EKC or U-50488, but are blocked by administration of mu agonists such as methadone, LAAM or diacetylmorphine. Kappa opiates, such as EKC and tifluadom, but not mu opiates, will attenuate the signs of U-50488 withdrawal [12].

The nature of the agonist and antagonist actions of drugs with both mu and kappa effects can be characterized to some extent in monkeys made dependent on either morphine or U-50488. Furthermore, the withdrawal signs that develop following chronic administration of agonist-antagonists can also provide evidence as to the nature of their opioid activity. In addition, the administration of relatively pure opioid antagonists to monkeys receiving an agonist-antagonist chronically may serve to support (and, perhaps, complicate) the information obtained following drug discontinuation.

The antagonist effects of buprenorphine were evidenced by its capacity to produce withdrawal signs in both morphine-dependent and U-50488-dependent monkeys [12]. It appeared to have little capacity to produce dependence on its own, however, since no withdrawal signs were observed following either abrupt discontinuation or naloxone administration in monkeys receiving buprenorphine chronically. Work by Dum et al. [13] suggested that dependence to buprenorphine does develop, but it is not easy to

TABLE I

DEPRIVATION-INDUCED WITHDRAWAL SIGNS

Morphine-Dependent Monkeys
Apprehension and aggression during handling
Abdominal twitching during handling
Abdominal defense reaction to palpation (cramping)
U-50488-Dependent Monkeys
General hyperactivity in cage
Excessive scratching
Excessive grooming of other monkeys
Yawning
Unusual tongue movements
Picking at fingers and toes

observe because the drug is difficult to displace from its receptor. Thus, special procedures are necessary to reveal buprenorphine's dependence capacity.

Studies of dependence to this and other mixed agonist-antagonists have been recently reviewed by Woods and Gmerek [14]. As they note, nalbuphine was also able to produce withdrawal signs when administered to morphine-dependent monkeys; chronic administration of nalbuphine resulted in mu-like withdrawal signs both on abrupt drug discontinuation and on administration of naloxone. Butorphanol neither suppressed nor exacerbated morphine withdrawal in morphine-dependent monkeys. Naloxone elicited severe morphine-like withdrawal signs in monkeys receiving butorphanol chronically, but when butorphanol was withdrawn abruptly, the withdrawal signs were more like U-50488 withdrawal than like morphine withdrawal. This somewhat anomalous profile of action may be due to the greater affinity of naloxone for the mu than the kappa receptor. A similar picture of naloxone-precipitated mu-withdrawal signs, and deprivation-induced kappa-withdrawal signs was produced by picenadol, although the naloxone-precipitated withdrawal signs were less severe during picenadol administration than were those produced during chronic butorphanol administration. Pentazocine, like butorphanol, did not alter the withdrawal signs in morphine-dependent monkeys. Pentazocine withdrawal signs, following pentazocine discontinuation or naloxone administration, were primarily kappa-like.

Kappa-like withdrawal signs were observed following discontinuation of chronic administration of cyclazocine and nalorphine [15]. Nalorphine precipitated withdrawal in monkeys dependent on U-50488, although the dose required to precipitate U-50488 withdrawal was much higher than that necessary to precipitate morphine withdrawal [12]. Bremazocine precipitated withdrawal in morphine-dependent monkeys, but suppressed withdrawal in U-50488-dependent monkeys [12].

Sedation

Although the effects of mu and kappa opioid agonists are clearly distinctive in tests of discriminative and reinforcing effects, and with measures of physiological dependence, with measures of analgesia and sedation there is overlap between the effects of mu and kappa opiates in the rhesus monkey. Even with these latter effects, however, distinctions can be made. As demonstrated in Fig. 3, the marked tolerance that develops to the sedative effects of U-50488 during chronic administration of this drug is not accompanied by cross tolerance to similar sedative actions of morphine [16]. There has, as yet, been little further evaluation of cross tolerance to mu and kappa agonists in the monkey. Measures of cross tolerance between U-50488 and other opioid agonists or agonist-antagonists should, however, help identify their action on kappa receptors. Likewise, measures of cross tolerance between morphine and other opioids would be expected to develop only to the extent that the other compound shares mu agonist activity.

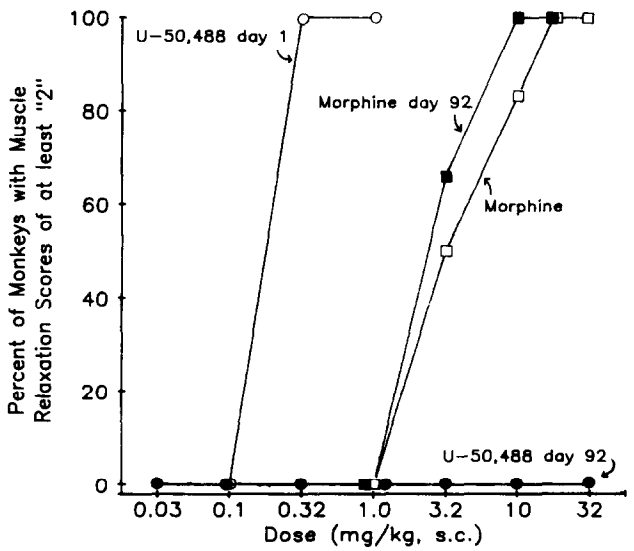

Fig. 3. The effect of U-50488 and morphine on muscle relaxation in monkeys receiving chronic injections of U-50488. U-50488 was given just prior to the first day of chronic administration (open circles; $n = 6$) and on day 92 of chronic administration (closed circles; $n = 3$). Morphine was given 1 week prior to the chronic administration of U-50488 (open squares; $n = 6$) and on day 92 of chronic U-50488 administration (closed squares; $n = 3$). From [16].

Analgesia

In addition to measures of reinforcing effects, discriminative stimulus effects, dependence producing potential, and capacity to produce or attenuate morphine withdrawal, agonist-antagonists have also been evaluated for their capacity to produce analgesia in the rhesus monkey. Tests for analgesia are extremely important, since analgesia is the clinical response for which these drugs are being evaluated. Analgesia in the rhesus monkey was indicated by measuring the time required for the monkey to pull its tail from a thermos of 50° or 55° water [17]. A cut-off time of 20 s set the maximum amount of analgesia. The water temperature has been shown to affect the amount of analgesia a given compound will produce; mu agonists were slightly more effective analgesics in 55° as compared to 50° water, whereas some kappa agonists were more effective analgesics when the water temperature was 50° [18].

As shown in Table II, using 55° water, the mu agonist morphine and the kappa agonists ethylketocyclazocine U-50488 and bremazocine each produced 100% analgesia in this assay.

Butorphanol and nalbuphine, included as mu agonists by virtue of their codeine-like discriminative effects, showed a partial agonism, as indicated by a less than 100% analgesic response.

Drugs that produce EKC-like discriminative effects are grouped as kappa drugs in Table II, and are segregated by their capacity to produce analgesia.

TABLE II

COMPARISON OF ANALGESIC EFFICACY AND POTENCY TO DISCRIMINATIVE POTENCY IN RHESUS MONKEYS

	% of maximum possible effect ($n = 10$)	Largest dose tested (mg/kg)	Dose necessary to produce discriminative effects equivalent to CODEINE	or EKC
Mu				
Agonists				
Morphine	100	10	1.0	
'Partial agonists'				
Butorphanol	76	10	0.1	
Nalbuphine	10	32	0.01	
Kappa				
Agonists				
Ethylketazocine	100	0.1		0.01
Bremazocine	100	0.1		0.001
U-50488	100	5.6		0.3
'Partial agonists'				
Cyclazocine	11	0.3		0.03
Levallorphan	4	10.0		0.10
'Antagonists'				
Oxilorphan	0	10.0		0.13
Nalorphine	0	320.0		0.32

As with the drugs acting on mu receptors, kappa drugs can be categorized as full or partial agonists or antagonists based on their capacity to produce analgesia in the tail-withdrawal assay. Cyclazocine and levallorphan each produced analgesia that was considerably less than that produced by EKC, U-50488, or bremazocine; oxilorphan and nalorphine produced no analgesia, even at very high doses. Kappa drugs with less analgesic effects should be able to produce partial (cyclazocine and levallorphan) or full (oxilorphan and nalorphine) antagonism of the analgesia produced by EKC, U-50488, and bremazocine. Likewise, butorphanol and nalbuphine should be able to antagonize, to some extent, the analgesia produced by morphine. These predictions are currently being explored in our laboratory.

DISCUSSION

It is clear from the above information that some of the different procedures used for evaluating opioids in the rhesus monkey do not demonstrate partial agonist properties of opioids that have both agonist and antagonist actions in other systems. It has been known for some time that the nature

of the preparation studied is important in indicating the various aspects of mu opioid action. The guinea pig ileum, for example, is more sensitive to the agonist actions of opioids than is the mouse vas deferens [19]. More thorough evaluation of the effects of opioids in different smooth muscle preparations indicated that the guinea pig ileum, mouse vas deferens, rat vas deferens, and rabbit vas deferens were quite different in their indication of the potency of mu and kappa agonist actions [20].

Similar differences in sensitivity to agonist and antagonist actions is clearly evident in behavioral preparations in the rhesus monkey. The effects of opioid agonists, antagonists and mixed agonist-antagonists have a profile of activity across different behavioral procedures in the monkey that appears to reflect, fairly directly, action at opioid receptors. There is clearly a need to explore more thoroughly the behavioral effects of mixed agonist-antagonists in order to explain, categorize and classify the actions of these drugs. It is possible that further descriptions of the actions of mixed agonist-antagonists will be possible by modifying the various behavioral procedures in use. Although drug discrimination procedures, as described in the rhesus monkey, do not demonstrate partial agonist effects of opioids, studies by Holtzman [21] and Colpaert [22] in the rat and by Koek (unpublished observations) in the pigeon indicate that partial agonist effects of opioids may be demonstrated quite clearly using drug discrimination procedures. One critical variable appears to be the dose of drug used as the training stimulus: if a relatively low dose is used to train the discrimination, drugs that have been shown to have partial agonist effects in other systems are more likely to appear as full or partial agonists in the drug discrimination paradigm. If a higher dose is used to train and maintain the discrimination, these same drugs are more likely to appear as antagonists. This capacity of lower training doses to reveal a partial agonist effect of various opioids may hold as well in drug discrimination procedures as used in the rhesus monkey, but this has not been carefully evaluated as yet.

The ability to change the sensitivity of a given preparation to the effects of opioids may have a parallel in studies with in vitro preparations. Smith [23] demonstrated that increasing the intensity of the electrical stimulus to the mouse vas deferens abolished the agonist effects of morphine, but not those of an opioid peptide that had full agonist effects. Thus, parametric changes in various preparations, both behavioral and in vitro, may assist in pointing out relative agonist and antagonist actions of various opioids.

In studies of opioids as reinforcers, it is also quite possible that changes in the schedule of reinforcement or its parameters could alter the threshold with respect to partial agonist effects of drugs. It is known that changes in the time-out following each delivery of drug will result in changes in the potency of the reinforcing effects of drugs (compare Ref. 24 to Ref. 25). Using different fixed-ratio values or using fixed-interval schedules of reinforcement could also shift the dose-effect curve [26]. It may thus be possible to

select parameters in these procedures that would demonstrate partial agonist effects.

The current procedure of evaluating the capacity of opioids to precipitate, reverse or exacerbate withdrawal in morphine-dependent monkeys is capable of demonstrating the antagonist effects of mixed agonist-antagonists. Drugs such as nalorphine, bremazocine, nalbuphine, and buprenorphine, which are full agonists of either the mu or kappa type in tests of discriminative effects, show mu antagonist effects in morphine-dependent monkeys. Even here, however, the parameters of dependence may determine the potency of antagonist action of the mixed agonist-antagonists. In humans made dependent on morphine, the dose used to establish morphine-dependence determined to some extent the drugs that produced morphine withdrawal [27]. Thus, altering the dose of mu or kappa agonist used to maintain dependence, and perhaps necessarily, developing more sensitive measures of withdrawal reactions, may assist in the behavioral characterization of mixed agonist-antagonists.

Measures of analgesia in the rhesus monkey provide some of the most interesting data about the mixed agonist-antagonist opioids. Here, partial agonist effects can be demonstrated in the pharmacologically appropriate way, by producing less than the maximum effect. Used in conjunction with tests of discriminative stimulus effects, where the nature of the receptor on which the drug acts can be easily determined, tests of analgesia apparently allow drugs to be ordered on the basis of their relative efficacy.

Interestingly, the analgesia measure of opioid effect in the monkey requires relatively higher doses of drug to produce a criterion response than does the measure of drug discrimination. As is shown in Table II, the dose of morphine required to produce a full agonist effect as an analgesic was 10 times higher than that required to produce a full agonist effect as a discriminative stimulus. The partial agonist, nalbuphine, produced full agonist effects in the drug discrimination procedure at a dose of 0.01 mg/kg, but was unable to produce a full agonist effect as an analgesic at a dose of 32 mg/kg. It is clear from these data that, under the experimental conditions used (i.e. with the specified training dose for drug discrimination and the specified temperature for analgesia), fewer receptors must be activated to produce the discriminative effect than must be activated to produce analgesia. As described by Miller et al. [20] for in vitro preparations, the amount of receptor reserve may differ considerably between these two procedures. What remains to be determined is the extent to which the potency of drugs will change as the parameters used to establish and maintain the behaviors involved are modified.

The data presented in this paper demonstrate that behavioral measures in the rhesus monkey vary in their capacity to indicate agonist, antagonist and partial agonist actions on the mu and kappa opioid receptor systems. When used in conjunction, these procedures allow a fairly complete picture to be drawn of the actions of individual drugs. It is possible that each of the

test systems can be modified in systematic ways so that more thorough descriptions can be made within a single procedure. It is clear, however, that different behavioral effects are profoundly modulated by the behavioral and pharmacological variables utilized.

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DISCUSSION

Dr. Lasagna: You showed a shift of the curve to the left of the kappa agonist after a mu antagonist. Is that a general phenomenon with other kappa-agonists and what's the explanation?

Dr. Woods: We've only tried beta-FNA with ethylketazocine, so I don't know how general it is. It really needs to be repeated a number of times with other agonists.

Dr. Yanagita: In your second slide and the last slide, you showed butorphanol as a mu agonist. But there are data showing a tremendous species differences between animals and humans. Even among animals, there are species differences. In animals, it is a mu agonist, but it also has antagonistic properties in rats. In the monkey, however, this antagonistic activity is very low. In addition, in humans, it doesn't look like a mu-type of drug.

Dr. Woods: I concur entirely with your point. I don't think that we should make gross generalizations about the nature of compounds until we have looked at a wide variety of species, measures, etc. I call butorphanol a mu, perhaps partial, agonist, because it has limited analgesic activity in this particular test, and it appears to be mu-like in its discriminative and reinforcing effects in monkeys. And I would think on the basis of those effects that at least there is an indication of it having some mu activity in the monkey.

Dr. Harris: I would like to make a comment and a question. First of all, I apologize if I ever gave the impression that the kappa drugs do not produce physical dependence. I meant dependence of the morphine-type. The question is that I'm confused by nalmefine being classified by you on the basis of its discriminative stimulus effects as a kappa agonist when we find nothing in the pharmacology of that compound which resembles so-called kappa activity at all. It's a mu agonist and antagonist, but we could see little behavioral activity. How do you explain its kappa actions in the discriminative stimuli paradigm?

Dr. Woods: The doses that are used in a drug discrimination assay with ethylketazocine are extremely small, so just a very marginal intrinsic activity may be sufficient to produce the discriminative stimulus effect. We intend to test that hypothesis by using different training doses and we should be able to make a differentiation. I'm nervous about that particular effect, as well, because I, too, am not aware of nalmefine having any kappa activity with an exception of this one behavioral assay.

Dr. Cook: Did you show, among the pure kappa agonists, greater intrinsic activity in producing analgesia in the monkey than with mixed agonist-antagonists?

Dr. Woods: That's right.

Dr. Cook: And was the difference that bremazocine produces 100%, which I assume is the cut-off, whereas a mixed-agonist produces only 10%?

Dr. Woods: It depends upon which mixed agonist you are talking about.

Dr. Cook: I think it was nalbuphine.

Dr. Woods: Nalbuphine is in a mu-category for us, because it has mu-agonist actions in the monkey.

Dr. Cook: So it produced what level of analgesia?

Dr. Woods: If I remember correctly, it was 10%.

Dr. Cook: O.K. But whether the kappa agonist is associated with mu or whether it's not, you see clear differences?

Dr. Woods: Yes. Their partial agonist actions do not depend upon what kind of receptor they are working at.

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