Tolerance and Cross-Tolerance to the Discriminative Stimulus Properties of Fentanyl and Morphine

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ABSTRACT

The investigation tested the hypothesis that tolerance would develop to the discriminative stimulus properties of fentanyl upon discontinuation of discrimination training and injection of fentanyl in doses larger than the training dose. Rats were trained to discriminate an injection of fentanyl, 0.04 mg/kg, from saline using a two-lever choice procedure with food as a reinforcer. Given acutely, morphine substituted for fentanyl and was 100-times less potent. Subsequently, training was stopped, and fentanyl, 0.08 mg/kg, was injected every 12 hr for 1 week. This procedure did not produce tolerance nor did tolerance occur when fentanyl, 0.16 mg/kg every 24 hr, was continued for an additional week. In contrast, a dose of morphine (8.0 mg/kg) that was equated for efficacy to the 0.08-mg/kg dose of fentanyl produced both tolerance to the morphine stimulus and cross-tolerance to the fentanyl stimulus after 3 to 4 days of administration. In an additional experiment, the time course for detection of fentanyl was found to be significantly shorter than the time course for the detection of morphine. These results suggest that the present, as well as a previous, report of failure to find tolerance to the stimulus properties of fentanyl is perhaps attributable to fentanyl's brief duration of action. To test this hypothesis, 16 rats were trained to discriminate fentanyl, 0.04 mg/kg, and dose-effect data were obtained for the generalization of fentanyl and the substitution of morphine for this discriminative stimulus. Subsequently, training was stopped and fentanyl was injected for 4 days in a design that called for injection of 0.12 mg/kg every 6 hr. This dosing regimen produced tolerance to the fentanyl stimulus and cross-tolerance to the morphine stimulus. Thus, tolerance can be obtained to the discriminative stimulus properties of fentanyl if dosing intervals are sufficiently brief.

Physical dependence and tolerance are hallmarks of drug dependence of the opioid type (Jaffe, 1980). Although this axiom has been well substantiated for the phenomenon of dependence and withdrawal, the evidence concerning the development of tolerance is more mixed, especially with regards to subjective effects of these drugs. Assuming that tolerance does in fact develop to the subjective effects of narcotics, then one might expect to see that users escalate their intake over time. This expectation has not been met in all cases: at least two studies have reported that drug intake in individuals dependent on narcotics tends to remain stable over time (McAluliffe and Gordon, 1974, Mirin et al., 1976). On the other hand, in studies conducted under controlled conditions, tolerance to the euphoric effects of narcotics has been obtained repeatedly (Haertzen, 1966; Haertzen and Hooks, 1969; Martin et al., 1977).

The study of subjective drug effects in humans is difficult, particularly when the drugs in question have high abuse liability and the experimental design requires high-dose long-term administration. Therefore, animal models of subjective drug effects may be useful for understanding this problem. In recent years, results from the drug discrimination procedure have shown that animals classify drugs in parallel to human reports of subjective drug-effects (e.g., Chait et al., 1986; see reviews by Schuster and Balster, 1977; Holtzman, 1983). Therefore, this paradigm may be particularly useful for studying a question such as tolerance.

With one exception (France et al., 1984), tolerance to the discriminative stimulus properties of morphine has been reported consistently when high doses of morphine have been given to subjects trained to detect this drug (Hirschhorn and Rosecrans, 1974; Shannon and Holtzman, 1976b; Miksic and Lal, 1977; Overton and Batta, 1979; Witkin et al., 1982; Sanders and Young, 1987). In contrast to the generally positive results found with morphine, Colpaert et al. (1976, 1978) reported that no tolerance developed to the discriminative stimulus properties of fentanyl in rats trained to detect fentanyl (Colpaert et al., 1978). This finding is surprising, because morphine and fentanyl have both been proposed to act predominantly through their agonist properties at mu-receptor sites (Martin and Sloan, 1977; Herz, 1984). In keeping with their similar receptor binding profile, these drugs share a wide variety of effects, including comparable subjective effects in humans (Gorodetzky and Martin, 1965). In animals, they have comparable properties when trained as discriminative stimuli: the stimulus properties of morphine substitute for fentanyl (Col-
hipaert and Janssen, 1986; Shearman and Herz, 1982); similarly, the stimulus properties of fentanyl substitute for morphine (Shannon and Holtzman, 1977a); in addition, the stimulus properties of both drugs are blocked by naloxone (Shannon and Holtzman, 1976a; Shearman and Herz, 1982; Wessinger and McMillan, 1986). Thus, with the exception that fentanyl is approximately 100 to 300 times more potent than morphine (Shearman and Herz, 1982; Colpaert and Janssen, 1986), results with these drugs are essentially interchangeable in the drug discrimination procedure, and it is not immediately clear why the two drugs should differ with regard to producing tolerance.

Colpaert et al. (1978) hypothesized that their failure to find tolerance to the discriminative stimulus properties of fentanyl was most likely attributable to methodological differences between their study and other studies investigating morphine tolerance. In three reports in which tolerance was found to the discriminative stimulus properties of morphine (Shannon and Holtzman, 1976b; Miskic and Lal, 1977; Wikkin et al., 1982) a procedure was used in which training on the discrimination was halted, and tolerance was induced by administering large doses of morphine. For example, Shannon and Holtzman (1976b) trained rats to detect 3.0 mg/kg of morphine; they then halted training and administered morphine, 10.0 mg/kg/12 hr, for 4 days. This procedure produced tolerance to morphine and cross-tolerance to methadone. In contrast, Colpaert et al. (1978) continued training with a low dose of fentanyl while also giving once-daily administrations of a higher dose of fentanyl. Even when doses up to 4 times the training dose were given daily for 3 weeks, no tolerance was detected. Colpaert et al. (1978) argued that their failure to obtain tolerance was most likely attributable to the continued training with a low dose of fentanyl during the period of high-dose administration. To account for the apparent tolerance seen in procedures where training was halted, Colpaert et al. (1978) proposed that injections of large doses of a drug during a period of nontraining results in “counter conditioning.” That is, the response to the training dose was decreased not through pharmacodynamic tolerance, but through either 1) extinction or 2) learning to attend to the larger magnitude of the cue produced by the large dose.

The hypothesis of Colpaert et al. (1978) has been challenged from several standpoints (Overton, 1984; Wood et al., 1984; Wood and Emmett-Oglesby, 1986; Järbe, 1986; Schechter, 1986); however, to date there has been no direct comparison of morphine and fentanyl in the same animals with regards to tolerance to their stimulus properties. More importantly, a prediction from the hypothesis of Colpaert et al. (1978) is that apparent “tolerance” should occur to the discriminative stimulus properties of fentanyl if training is suspended and subjects are injected with fentanyl in doses higher than the training dose. The highest dose of fentanyl used by Colpaert et al. (1978) in their failure to obtain tolerance was 4-fold greater than that of the training dose, and it was given once daily. Therefore, in an initial study the present experiments used this parameter as an upper limit in an attempt to obtain tolerance to the stimulus properties of fentanyl. Subsequently, additional experiments were performed to equate doses of fentanyl and morphine operationally and then to test for direct comparisons of their ability to produce tolerance and cross-tolerance.

Methods

Subjects. Twenty-four male Wistar rats (Max-Planck-Institute breeding colony) were housed individually. Body weights were main-

tained at 320 ± 10 g by limiting daily access to food; water was freely available except during sessions in the operant chambers. Before the studies described as Experiment 1 to 3, subjects were used to determine substitution of mu and kappa agonists for the fentanyl training stimulus (reported in Emmett-Oglesby and Herz, 1987). Each subject was tested with no more than three drugs in that study, and all subjects were trained on the discrimination for at least 10 additional sessions before the experiments described below were conducted.

Apparatus. Discrimination training was conducted in standard operant chambers (Coulbourn Instruments Inc., Bilaney Consultants, Dusseldorf, FRG) as described in detail in Lal and Emmett-Oglesby (1983). These chambers contained two levers mounted on a wall with a magazine for food delivery located between the levers. Food reward (45 mg pellets, Bio-Serv Inc., Bilaney Consultants) was delivered by a pellet dispenser. Recording of lever responses and scheduling of rein-forcement contingencies were performed through an IBM-compatible microcomputer (SUPER PC, Special Electronic, Munich, FRG) con-

ected to the chambers through LVB interfaces (Med Associates, East
Fairfield, VT) using an IBM-PC modified version of a program de-
scribed previously (Emmett-Oglesby et al., 1982; Spencer and Emmett-
Oglesby, 1985).

Discrimination training. With food as a reinforcer, subjects were trained to press the left lever, and their behavior was shaped progressively until 10 lever-press responses (fixed-ratio 10) were required to obtain reinforcement. Subsequently, this same procedure was repeated for the right lever. When preliminary shaping was completed, the drug lever was assigned as the left lever for half of the subjects and as the right lever for the other half of the subjects. Next, all subjects were trained to press the drug lever 30 min after injection of fentanyl, 0.04 mg/kg s.c., and the saline lever 30 min after injection of saline, using the procedure described by Emmett-Oglesby and Herz (1987). In this procedure, fentanyl and saline sessions are presented in equal numbers, in a sequence such that fentanyl or saline sessions never occurred more than twice in succession. In addition, subjects were trained more than once daily whenever a saline training session started the day. Thus, whenever a saline training session occurred, immediately upon its completion subjects were injected with the next condition that was due to be trained (either fentanyl or saline), and they were then retrained. In this fashion, on a given day, a subject could receive either 1) fentanyl, 2) saline and then fentanyl or 3) saline, then saline and then fentanyl and be trained accordingly. On average, subjects were thus trained twice per day. Until testing was initiated, subjects were trained daily. Subsequently, training and testing were conducted at least 5 days per week. Acquisition curves for the discrimination of fentanyl by these subjects can be found in Emmett-Oglesby and Herz (1987).

Only responses emitted before obtaining the first reinforcer were used to determine which lever was selected, and the first lever on which 10 responses occurred was considered the selected lever. Discriminative control was defined as 10 successive sessions of correct lever selection. Once this criterion was achieved, training was continued for at least 10 additional sessions before testing began.

Discrimination testing. Testing procedures were identical to training procedures except that 10 responses on either lever produced food reinforcement, and sessions were conducted only until one reinforcer was obtained or until 10 min had elapsed. The lever on which 10 responses were first emitted was recorded as the selected lever. In these tests, all doses were tested during a single day using an ascending series of drug injections (Emmett-Oglesby and Herz, 1987; Paule and Wenger, 1986; Wenger, 1980). Starting doses for these tests (0.01 mg/kg of fentanyl and 1.0 mg/kg of morphine) were taken from previously published results (Shearman and Herz, 1982), and tests were conducted for the starting doses as described above. Immediately upon completion of a test, twice this dose was administered, and subjects were retested 30 min later. This procedure was continued until full generalization to the training stimulus occurred. Data from these tests are presented as a cumulative dosing regimen (each dose is added to the preceding dose(s) to obtain the calculated dose).

Experiment 1: effect of suspending training and injecting
fentanyl on the development of tolerance for the discriminative stimulus produced by fentanyl. Dose-effect data for the generalization of fentanyl (0.01, 0.02 and 0.04 mg/kg) were determined in 16 rats. Subjects were then trained for five additional sessions and, subsequently, training was halted and the rats were injected with fentanyl (0.08 mg/kg/12 hr). After 7 days of this treatment, the dose-effect curve for the detection of the fentanyl stimulus was redetermined, 12 hr after the last injection of 0.06 mg/kg of fentanyl. After this test, rats were injected with 0.16 mg/kg of fentanyl every 24 hr for the next 7 days, and no training occurred during this period. The fentanyl dose-effect curve was again redetermined 24 hr after the last 0.16-mg/kg injection.

Experiment 2: substitution of morphine for fentanyl and determination of tolerance and cross-tolerance for morphine and fentanyl. Rats participating in the previous study were retrained for 2 weeks, and subsequently dose-effect data were reobtained for fentanyl in all 24 subjects. Next, a dose-effect curve was determined for the substitution of morphine for the fentanyl discriminative stimulus in all 24 subjects. Subsequently, training was halted and rats were assigned to two groups (N = 10 and 11, respectively) that had similar dose-effect curves for the detection of these two stimuli, and these groups then received either fentanyl, 0.08 mg/kg, or morphine, 8.0 mg/kg, every 12 hr. These doses were chosen as being equivalent because they were double that which produced 100% fentanyl-lever selection (0.04 mg/kg of fentanyl; 4.0 mg/kg of morphine). After 3 days of this injection regimen, the dose-effect curve for fentanyl was redetermined in the group receiving chronic fentanyl, and the dose-effect curve for morphine was redetermined in the group receiving chronic morphine. Twelve hours later the groups were injected with their chronic treatment (either fentanyl, 0.08 mg/kg, or morphine, 8.0 mg/kg), and 12 hr after this the dose-effect curve for morphine was redetermined in the group receiving chronic fentanyl, and the dose-effect curve for fentanyl was redetermined in the group receiving chronic morphine.

Experiment 3: duration of fentanyl and morphine as discriminative stimuli. Rats participating in Experiment 2 were tested daily for the detection of the training stimulus of 0.04 mg/kg of fentanyl. When these tests produced greater than 90% of the subjects selecting the fentanyl lever (4 days), subjects were then retrained on the discrimination for an additional 2 weeks. Subsequently, fentanyl, 0.04 mg/kg, was injected in 24 rats, and they were tested for their detection of a fentanyl stimulus at 30 min, 1, 2 and 3 hr postinjection. For tests at more than 1 hr after the initial injection, 1 ml/kg of 0.9% saline was injected 30 min before each test. Subjects were retrained for four sessions, and then this experiment was repeated using 16 rats and a fentanyl dose of 0.16 mg/kg. After 7 days of additional training the experiment was again repeated using 21 rats injected with morphine, 16.0 mg/kg.

Experiment 4: tolerance to fentanyl and cross-tolerance to morphine obtained by giving fentanyl every 6 hr. Sixteen subjects, naïve to experimental treatment, were trained to detect fentanyl, 0.04 mg/kg, using the procedure described above. They were trained for 60 sessions, and then dose-effect data were obtained for the generalization of fentanyl to, and the substitution of morphine for, the training stimulus. After retraining for an additional week, training was halted and fentanyl injections were started in a design that called for 0.12 mg/kg/6 hr of fentanyl administered for 4 days. This dose was picked as one that would be likely to produce sustained quantities of fentanyl in the blood while not compromising the health of the subjects. However, after the second dose of fentanyl, four rats had to be removed from the study. The remaining animals were injected with a dose of 0.06 mg/kg at the third and fourth scheduled injections, and then they were returned to the 0.12 mg/kg/6 hr regimen without further health difficulties (daily allotments of food were consumed within 6 hr of access; no weight loss occurred; and no respiratory difficulties were noted). After 3 days of this regimen, tests were conducted in place of one of the regularly scheduled fentanyl injections. For these tests, rats were assigned to two groups (A and B) of six subjects each. In group A, dose-effect data were reobtained for fentanyl, and in group B, dose-effect data were reobtained for morphine. Subsequently, the three final scheduled injections of 0.12 mg/kg 6 hr of fentanyl were given, and dose-effect data were again redetermined, but group A was tested with morphine, and group B was tested with fentanyl.

Data analysis. Discrimination data are presented in terms of percentage of subjects selecting the drug lever, which is the percentage of subjects emitting 10 responses on the drug lever before emitting 10 or more responses on the saline lever. For analysis of dose-effect data, responses used to determine lever-choice were converted to percentage of drug-lever responding, and these scores were tested using a repeated measures analysis of variance.

Drugs. Fentanyl citrate (Janssen Pharmaceutica, Beere, Belgium) and morphine HC1 (Merck Chemical Co., Darmstadt, FRG) were dissolved in 0.9% saline and given s.c., 30 min presession. All doses were calculated in terms of the free base.

Results
Acquisition of stimulus control. Subjects required approximately 40 sessions of training to discriminate fentanyl (0.04 mg/kg) from saline and meet the criterion of selecting the correct lever on 10 consecutive sessions. They were trained for an additional 10 sessions before any dose-effect testing occurred, and they received approximately 50 additional training sessions before chronic administration experiments started. At the onset of chronic administration experiments, the error rate in saline and fentanyl training sessions was less than 3%.

Detection of fentanyl before and after chronic administration of fentanyl. When tested acutely, fentanyl produced a dose-related (0.01–0.07 mg/kg) generalization to the training stimulus (fig. 1). The cumulative dosing method required a dose of 0.07 mg/kg to produce full substitution for the training stimulus (0.04 mg/kg). This dose (0.07 mg/kg) was calculated by adding the preceding doses given during the cumulative

![Graph](image-url)
dosing procedure, and the fact that it is higher than the training dose suggests that either some degree of tolerance develops within the test session, or that fentanyl is metabolized so rapidly that the cumulative dose procedure overestimates the quantity of fentanyl present at the time of testing.

The detectability of the fentanyl cue was neither enhanced nor diminished when training was terminated and fentanyl was administered in doses 4-fold larger than the training dose for 2 weeks (fig. 1). For the first week of these treatments, injections were given in divided doses of 0.08 mg/kg every 12 hr. When dose-effect redetermination revealed no tolerance, the dose of chronic administration was modified to once daily administration of 0.16 mg/kg for 1 week. At the end of this period, dose-effect redetermination again showed no evidence for tolerance.

Detection of fentanyl and morphine before and after chronic administration of either fentanyl or morphine. In acute tests, morphine produced a fentanyl-like cue, but it was about 100 times less potent than fentanyl in the production of this cue (data not shown). Subsequently, rats were assigned to two groups equated for their detection of these two stimuli (open symbols in figs. 2 and 3), and operationally equivalent doses of these drugs were selected for chronic administration. These doses were equated with regard to morphine being approximately 100-fold less potent. Thus, rats in one group received fentanyl, 0.08 mg/kg every 12 hr, and rats in the other group received morphine, 8.0 mg/kg every 12 hr. Because the smallest doses in the dose-effect curves (0.01 and 1.0 mg/kg of fentanyl and morphine, respectively) produced little or no fentanyl-lever selection under acute treatment conditions, only the next 2 doses (0.03 and 0.07 mg/kg of fentanyl and 3.0 and 7.0 mg/kg of morphine) were used in statistical tests to determine if chronic treatment produced tolerance. Chronic fentanyl produced neither tolerance to the stimulus properties of fentanyl nor cross-tolerance to the stimulus properties of morphine (fig. 2). In contrast, morphine produced both tolerance to the stimulus properties of morphine and cross-tolerance to the stimulus properties of fentanyl (fig. 3).

Detection of fentanyl and morphine as a function of time after administration. A training dose of fentanyl, 0.04 mg/kg, produced a discriminative stimulus that declined to essentially no effect within 2 hr (fig. 4). Quadrupling this dose of fentanyl only increased the duration of the fentanyl stimulus by approximately 1 hr (fig. 4). In contrast, a dose of morphine 4-fold greater than the dose producing 100% fentanyl-lever selection produced a much longer lasting stimulus (fig. 4).

Tolerance to fentanyl and cross-tolerance to morphine when fentanyl is given every 6 hr. In acute tests, fentanyl generalized to the fentanyl training stimulus in a dose-dependent manner; morphine again substituted for fentanyl, and morphine was about 100-times less potent than fentanyl in the production of the cue (O vs. □ in fig. 5). Rats were then injected with 0.12 mg/kg/6 hr of fentanyl, and fentanyl and morphine dose-effect data were redetermined on days 3 and 4 of chronic fentanyl administration. This dosing regimen of fentanyl produced tolerance to fentanyl (○ vs. □, fig. 5) and cross-tolerance to morphine (□ vs. □, fig. 5).

Discussion

Acutely, morphine and fentanyl produced comparable discriminative stimuli, but morphine was approximately 100-fold less potent, which is in agreement with previous results (Shannon and Holtzman, 1977a; Shearman and Herz, 1982). Thus, in a cumulative dosing procedure, 7.0 mg/kg of morphine was found to be approximately equivalent to 0.07 mg/kg of fentanyl. When double this quantity of morphine was administered every
of tolerance to morphine appears to be nearly proportional to the dose of morphine administered. In addition, tolerance to morphine produced cross-tolerance of a similar magnitude to fentanyl. These effects developed after brief periods of morphine administration; moreover, morphine does not induce either its own metabolism or that of drugs from different chemical classes (Martin and Sloan, 1977). Therefore, we suggest that the present results with morphine are most readily attributable to a pharmacodynamic mechanism of tolerance. Cross-tolerance to fentanyl in this experiment, and to methadone previously (Shannon and Holtzman, 1976b), suggests that the mechanism probably extends to all drugs possessing mu-agonist properties.

The present results are generally compatible with those of previous investigations showing tolerance to the discriminative stimulus properties of morphine when morphine is given in high doses. Tolerance has been found when training has been continued during the time of supplemental high-dose morphine administration (Hirschhorn and Rosecrans, 1974; Young and Sannerud, 1987), and an even greater degree of tolerance has been obtained when morphine was given in high doses with no additional training on the discrimination before tests of tolerance (Shannon and Holtzman, 1976b; Miksic and Lal, 1977; Witkin et al., 1982; Sannerud and Young, 1987). These generally positive results can be contrasted with those obtained by France et al. (1984), who trained pigeons on a morphine discrimination, then halted training and administered morphine daily for 5 days in a nearly 20-fold higher dose than that used for training, but did not find tolerance. France et al. (1984) did not speculate on reasons for why their experiment might have failed to obtain tolerance, and the present investigators also are unable to explain this previous finding. Thus, the weight of evidence is that high-dose morphine administration does produce tolerance to its stimulus properties, but this conclusion needs to be verified.

In contrast to the results found with morphine, termination of training and administration of fentanyl, 0.08 mg/kg/12 hr for 1 week, did not result in tolerance to the discriminative stimulus properties of fentanyl. When this experiment was extended and modified such that a dose of fentanyl 4-fold greater than the training dose was administered once daily for 1 week, again no tolerance was obtained. Thus, after 2 weeks during which subjects were withheld from training and injected daily with 4 times the training dose (first in divided doses and then in a single daily dose), no tolerance developed to the fentanyl stimulus. This result is comparable to that obtained by Colpaert et al. (1979), who reported that, even after 3 weeks of 0.16 mg/kg of fentanyl given once daily, they were unable to obtain evidence for tolerance to the stimulus properties of this drug. However, Colpaert et al. (1978) suggested that their failure to find tolerance was related to a procedural variable in their experiment; that is, animals were continued on discrimination training with low doses of fentanyl during the time of administration of high dose of fentanyl. The present results do not support the hypothesis of Colpaert et al. (1978) because in the present experiment training was terminated during the period of high-dose fentanyl administration, but still no tolerance was observed. It therefore seems likely that another variable may account for the present results and those obtained previously by Colpaert et al. (1978).

The present data suggest that the key difference between fentanyl and morphine with regard to their ability to produce
tolerance is most likely attributable to their differences in duration of action. It is well established that pharmacodynamic tolerance occurs only when a sufficient dose of drug is present in the subject for a sufficient period of time (Martin, 1970; Kalant et al., 1971; Jaffe, 1980). As shown in the present experiment, when used as discriminative stimuli, morphine has a much longer duration of action than fentanyl, and this observation is in keeping with the well known differences between these drugs with respect to their duration of analgesic activity (Hess et al., 1972) and their elimination half-lives (Berkowitz et al., 1974; Hug and Murphy, 1981); thus, it is likely that in the experiments in which fentanyl was given once or twice daily, the drug was not present in the subjects for a sufficient period to produce tolerance. This hypothesis was tested directly in an experiment in which doses of fentanyl 3-fold higher than the training dose were administered every 6 hr for 4 days. These dosing parameters were selected in order to maximize the duration of daily exposure to fentanyl. This dosing regimen produced tolerance to fentanyl and cross-tolerance to morphine after only 3 to 4 days, which is in keeping with the time course for development of tolerance to the discriminative stimulus properties of morphine (present experiment, and previous report by Shannon and Holtzman, 1976b). The variables of increased dose and increased frequency of dosing were confounded in the present study, but independent of which of these factors produced tolerance, it is likely that the single daily dose of 0.16 mg/kg of fentanyl used in a previous experiment (Colpaert et al., 1978) was insufficient to produce tolerance. Supporting evidence also is available suggesting that the duration of drug action is a critical variable for producing tolerance to the discriminative stimulus properties of drugs. Wood and Emmett-Oglesby (1986) reported that when equated for efficacy in a cocaine discrimination, injections of amphetamine produced greater tolerance than injections of cocaine, a result that was attributed to the longer duration of action of amphetamine.

Colpaert et al. (1978) argued that their single daily dose of fentanyl was sufficient to produce tolerance to the stimulus properties of the drug, because parallel measures showed that this injection regimen produced tolerance to analgesic effects of fentanyl. However, the relationship between the analgesic properties and the stimulus properties of opioids is not well established. In experiments testing central injection of opioids, brain regions that have been established as important in mediating analgesia were not found to be involved in the mediation of the discriminative stimulus (Shannon and Holtzman, 1977b). Thus, tolerance to analgesia appears to be separable from tolerance to subjective effects. Indeed, it also may be the case that physical dependence may be separable from tolerance to subjective effects; a recent report by Gaiardi et al. (1986) shows that single daily doses of morphine are capable of maintaining dependence without affecting stimulus detection.

In summary, the present results are consistent with the hypothesis that pharmacodynamic tolerance occurs to the discriminative stimulus properties of opioids. We suggest that failure to tolerance to fentanyl in this and in previous experiments can be attributed most parsimoniously to the very brief duration of action of this drug. When this hypothesis was tested directly by increasing the number of fentanyl injections given each day, tolerance to the stimulus properties of fentanyl was obtained rapidly. Thus, drug discrimination studies in animals may provide a useful model for studying pharmacodynamic tolerance to a subjective drug effect.

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