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Evidence of Place Conditioning After Chronic Intrathecal Morphine in Rats

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ADVOKAT, C. *Evidence of place conditioning after chronic intrathecal morphine in rats.* PHARMACOL BIOCHEM BEHAV 22(2) 271–277, 1985.— The acute administration of either systemic or intrathecal morphine produced an antinociceptive reaction on the tail flick test; only systemic morphine produced a sedative effect on motor activity. Rats receiving chronic intrathecal injections were hyperactive relative to saline injected control subjects. After a series of four injections, a place preference was induced by both routes of administration: rats who had previously received morphine either by subcutaneous or intrathecal injection spent significantly more time in the context in which the drug had been given, relative to rats who were comparably injected with saline. These data suggest that chronic intrathecal morphine in rats may elicit a discriminable cue, either through direct pharmacological stimulation of supraspinal sites, or, indirectly, as a consequence of spinal opiate action.

Place conditioning Intrathecal morphine Tail flick Rats

THE effective management of acute and chronic pain remains a major medical challenge. That challenge is most often met by the administration of opiates and other pharmacologically related compounds. Unfortunately, there are two significant factors which limit the use of these drugs. First, there is the problem of side effects, including sedation, nausea and vomiting, urinary retention and sensory disturbances, as well as the potential for life threatening respiratory depression. Second, there is the assumed risk of tolerance and/or dependence [12]. Although it has been argued that this danger is often exaggerated, [13, 16, 18, 21] much effort has been expended in finding ways of minimizing the risk.

As a result, great interest was generated by recent reports of selective and prolonged analgesia following epidural or intrathecal opiate injection [26, 30, 36].

The spinal route appeared to be particularly advantageous because profound analgesia was obtained in animals without any changes in vegetative function (respiration, sedation, feeding, heart rate, blood pressure or urinary retention). Moreover, histological examination using dyes and radioactive markers indicated that there was minimal spread within the intrathecal space after a single injection [33, 34, 35]. Within the last few years, the long-lasting analgesia elicited by spinal opiates in animals has been successfully replicated in numerous clinical trials.

Unfortunately, the initial enthusiasm generated by these results was soon tempered by the realization that all the standard opiate side effects could still be induced by spinal opiate administration, particularly pruritis (itching), urinary retention, nausea and vomiting and, most critical, respiratory depression [4, 5, 7, 10, 22]. The elicitation of such side effects as nausea, vomiting and respiratory depression suggests that drugs which are administered to the spinal cord may eventually gain access to higher brain centers [7].

In contrast, however, to the prevalence of these untoward reactions, there have been no comparable reports of any positive side effects (e.g., euphoria) following spinal morphine. This lack of evidence for the pleasurable side effects of spinal opiates raises the question of whether chronic spinal opiate administration induces a consciously discriminable drug cue and if so whether such a stimulus is positively reinforcing. The present experiments were designed to address this issue by examining the locomotor and reinforcing effects of spinal (intrathecal) and systemic morphine in rats.

The reinforcement potential of spinal and systemic morphine was assessed by the place conditioning method. In this procedure, subjects are repeatedly exposed to a pharmacological agent in the presence of distinctive environmental cues. After several pairings of the compound with a specific context, the animals are allowed to choose between the environment that was previously paired with the drug and an alternate environment that was not. The amount of time spent in the drug context is compared with the time spent in the non-drug context. If the drug context is subsequently avoided the drug is presumed to be aversive; if the drug context is preferred the drug is presumed to be reinforcing.

This procedure has been utilized to assess the reinforcing properties of several compounds. Rats exposed to emetics such as γ- and X-ray irradiation [9] and apomorphine [3] as well as other agents, such as ethanol [8,28] while restricted to a distinctive context, subsequently avoided that environment. In contrast, several reports have shown that rats spend more time in an environment paired with morphine and other opiates than in one paired with saline [2, 14, 15, 19, 23, 24, 27]. In a recent extensive series of experiments, Mucha and his colleagues found that a place preference could be conditioned not only to systemically administered opiates, but also to microinjection of morphine directly into the brain [19,27]. Therefore, the place preference test was chosen as a reliable and sensitive technique for examining the reinforcing properties of intrathecal morphine.

A preliminary account of some of these data was presented previously [1].

METHOD

Subjects

A total of 91 male, Sprague Dawley derived rats (King Labs, Oregon, WI) completed the experiments. The rats weighed approximately 400 g when they arrived at the animal colony, at which time they were housed three to a cage with ad lib access to food and water. After one to seven days in the colony the rats were catheterized (see below) after which they were housed individually so that the catheters would not be destroyed by their cagemates.

Spinal Catheterization

The surgical procedure was derived from the method of Yaksh and Rudy [32]. The animals were anesthetized with ether throughout the procedure and mounted on a conventional stereotaxic instrument. The surgical technique consisted of exposing the back of the skull so that an incision of the atlanto occipital membrane could be made through which polyethylene tubing (PE-10) was inserted 8.0 cm into the spinal subarachnoid space. The tip of the externalized catheter was melted closed with a soldering iron; when spinal injections were made the tip was snipped off and remelted if necessary for chronic administration. Animals were given 7 to 10 days of recovery before the start of an experiment. Autopsies were performed at the end of each experiment to insure proper placement of the catheter. Any animal with a catheter inadvertently placed inside the spinal cord was not included in the data analysis.

Drugs

For intrathecal administration morphine sulfate (Merck, Rahway, NJ) was dissolved in 0.9% sterile physiological saline and injected in a total volume of 10 μl followed by a 5 μl wash of saline. The injections were given by manual operation of a Hamilton microsyringe over a 20–30 sec period. For systemic administration morphine sulfate was dissolved in 0.9% physiological saline and injected subcutaneously in a volume of 0.1 ml per 100 g of body weight. In each case, the same volume was used for the respective control injections.

Tail Flick

The tail flick (TF) response was used as a nociceptive index. Noxious stimulation was produced by a beam of high intensity light focused on the tail. The response time was measured automatically and was defined as the interval between the onset of the heat stimulus and the abrupt flick of the tail. Each determination consisted of three trials; the mean score was taken as the response latency. Animals not responding within 14 sec were removed from the apparatus and assigned a response latency of 14 sec.

Activity

The locomotor effect of morphine was defined as a change in activity following drug administration. Locomotor activity was assessed by measuring the latency of each animal to cross from one side of a shuttlebox to the alternate side. The shuttlebox consisted of a rectangular chamber 21.5 cm wide, 55 cm long and 35 cm high. Five sides, including

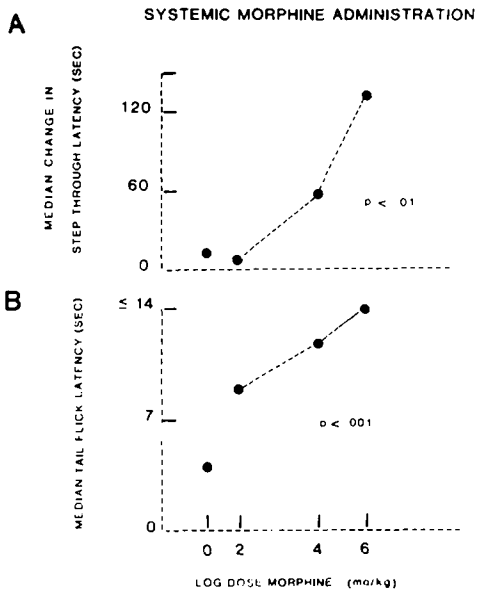

FIG. 1. A: Median change in shuttle box step-through latency, from pre-drug baseline of rats (n=5–10) 40 min after a morphine (2, 4 or 6 mg/kg, SC) or saline (0 mg/kg, SC) injection. B: Median tail flick latency of the same rats, obtained immediately after the step-through latency.

the hinged top, were constructed of wood, the sixth was Plexiglas and provided a window through which the rat could be observed. A raised metal grid floor ran along the length of the box. The chamber was divided in half by a metal wall through which a sliding door 10 cm high and 8 cm wide was cut.

On the first day of the experiment, all rats received one 10 min habituation trial in which they were allowed free access to the two shuttlebox compartments. On the following day a single baseline step-through (ST) latency was obtained. Successive rats were alternately placed on each side of the shuttlebox and were considered to have crossed the compartment when all four paws were on the opposite side. A ceiling of 300 sec was placed on the response.

On the basis of this initial pre-drug latency the rats were assigned to the various drug groups in a counterbalanced sequence such that all groups would have an equal average baseline step-through latency. On the third experimental day a second latency was determined for each rat at a specified time point after morphine or saline administration. The difference between the pre- and post-drug latencies represented the drug induced change in activity. An increase in step-through latency indicated a decrease in locomotion and defined sedation.

At the end of this second, post-drug, latency test, each rat was evaluated for nociceptive responsivity on the tail flick test. This procedure was done to confirm the analgesic efficacy of the morphine injections.

Place Conditioning

Each animal was placed in the previously described shuttlebox for 10 min a day for five days. In this experiment the two compartments of the shuttlebox differed with respect to the floor of the chambers. One compartment had a grid

floor, the other had a black rubber mat placed over the grid floor. The rats were alternately placed in each of the two compartments during their five successive preexposures to the shuttlebox. The number of seconds spent in each compartment was recorded and on the fifth day a determination was made as to which of the two compartments, if any, was preferred by each rat.

After this initial preference was determined drug administration was begun. The rats were divided into two groups with matched preference scores. Each rat was first restricted for one hour a day to the preferred compartment of the shuttlebox, then injected with either morphine or saline, and then restricted for a second hour to the nonpreferred side of the shuttlebox. This manipulation was repeated daily for a total of four trials. Animals injected systemically received four injections of 3 mg/kg SC of morphine or an equal volume of saline, animals injected intrathecally (ITH) received four injections of 30 μg/10 μl of morphine or an equal volume of saline.

On the fifth day no injections were made. Each rat was placed in the previously preferred compartment and allowed free access to the alternate side. The amount of time spent during the 10 min test period in the previously nonpreferred compartment was recorded for each rat.

At the end of this test, all rats participating in these experiments were assessed on the tail flick test, to determine whether there was any detectable analgesic effect of the previous morphine injections.

Data Analysis

The results were evaluated with nonparametric statistics, specifically; the Kruskal-Wallis one-way analysis of variance (for differences among the groups) the Mann-Whitney U-test (for differences between groups) and the Spearman rank correlation coefficient [25]. Nonparametric tests were required because in many instances the cut-off scores imposed on the behavioral tests were reached by several subjects. The accepted level of significance was $p<0.05$, and unless otherwise indicated, all tests were two-tailed.

RESULTS

The Effect of Acute Morphine Administration on Locomotion and Nociception

Systemic injection. The acute, dose dependent effect of subcutaneously injected morphine on shuttlebox step-through latencies and on tail flick latencies is shown in Part A and Part B, respectively, of Fig. 1. As indicated in the figure the latencies on each of the two tests increased significantly as a function of increasing drug dose. Step-through latencies were elevated as the dose was increased ($H(3)=12.7$, $p<0.01$). Individual comparisons revealed that there was no difference in latency between the saline ($n=10$) and the 2 mg/kg dose ($n=5$) but that both the 4 mg/kg ($n=5$) and the 6 mg/kg ($n=7$) dose resulted in a significant increase in latency ($U=2.5$, $p<0.02$ and $U=4.0$, $p<0.002$, respectively).

A similar pattern was obtained with tail flick latency. The difference among the four groups on the analgesic assay was significant ($H(3)=20.3$, $p<0.001$). In this case, however, all three drug doses differed significantly from the saline condition ($U=5$, $p<0.02$; $U=0$, $p<0.002$; $U=0$, $p<0.002$, for 2, 4 and 6 mg/kg, respectively).

These results, therefore, indicate that shuttlebox latency is a useful index of locomotor activity and that it is sensitive to modulation by systemically administered morphine. The data support the expectation that subcutaneously administered morphine induces both, analgesia and sedation. Comparison of the results from the two behavioral assays suggests that tail flick analgesia can be produced by a dose of morphine, e.g., 2 mg/kg, that is too low to produce an overt influence on motor activity.

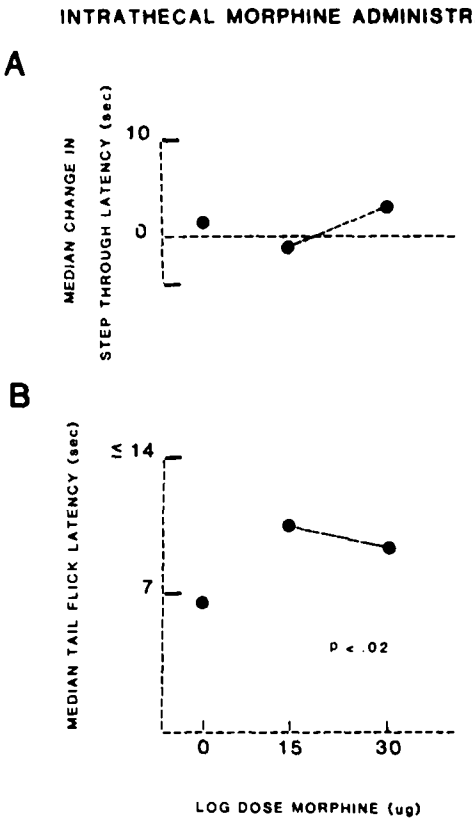

FIG. 2. A: Median change in shuttlebox step-through latency, from pre-drug baseline of rats ($n=5$ or 6), 40 min after an ITH morphine (15 or 30 μg) or saline (0 μg) injection. B: Median tail flick latency of the same rats, obtained immediately after the step-through latency.

Intrathecal (ITH) injection. The acute effect of intrathecally administered morphine on shuttlebox step-through latencies and on tail flick latencies is shown in Part A and Part B, respectively, of Fig. 2. As indicated in Part A of the figure, there was no evidence of a sedative effect of spinal morphine. The latencies of the drug groups were not different from the latency of the saline, control group.

Intrathecal morphine injections did, however, produce an increase in tail flick latencies. There was a significant difference among the three groups on this analgesic assay ($H(2)=8.4$, $p<0.02$). Individual comparisons revealed that the saline group ($n=5$) differed from each of the two drug groups, 15 μg ($n=6$) and 30 μg ($n=5$) ($U=3$, $p<0.03$ and $U=4$, $p<0.048$, one-tailed; respectively). There was no difference between the two drug groups. The results indicate that an acute ITH morphine injection can elicit analgesia without modifying motor activity.

Interestingly, in contrast to the lack of correlation between analgesia and locomotion after ITH morphine, a relationship between TF and locomotion was observed after saline injection. The data indicated that the latencies of the

two tests were positively correlated in the control group. This observation was confirmed by the calculation of a Spearman rank correlation coefficient ($r_s=1.0$, $n=5$, $p<0.02$). That is, saline injected animals who had long latencies in the shuttlebox also had long latencies on the tail flick test. Whether this result is a function of some direct physiological influence of saline injections, or, alternately perhaps, a generalized reflection of stress induced "analgesia" remains to be seen.

In summary, these results indicated that a single acute injection of intrathecal morphine did not reduce motor activity within 30–40 min even though such treatment produced analgesia. It was possible, however, that locomotion would be depressed at longer post-injection intervals. Therefore, the next experiment examined the motoric and analgesic effects of an acute injection of 30 μg of morphine at two additional time points, 3 and 6 hours, after injection. The results of this experiment are summarized in Fig. 3, which shows the change in step-through latency (Part A) and the tail flick latency (Part B) of rats who were tested either 0.5 (data from previous study), 3 or 6 hours after a spinal injection. As indicated in the figure, there was no evidence of any change in step-through latency within 6 hours after a single 30 μg morphine injection. There was also no difference in TF latency among the three groups tested at each of the three intervals. This result implies that the analgesic influence of ITH morphine does not diminish within six hours after injection.

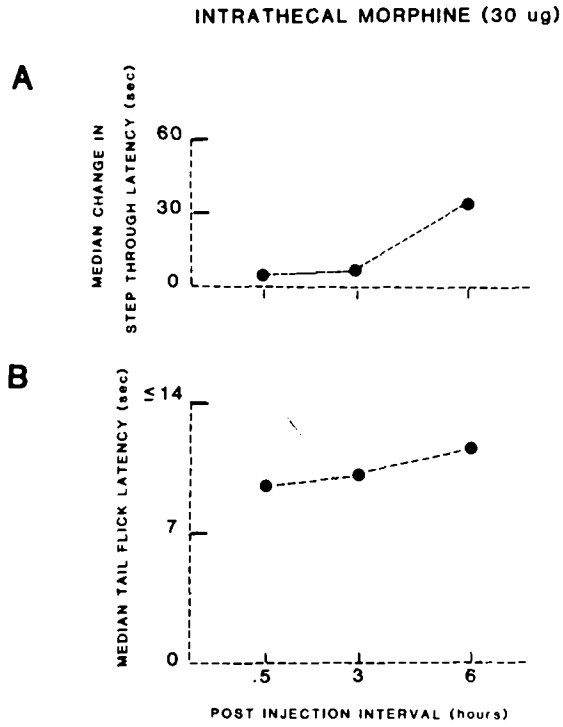

FIG. 3. A: Median change in shuttlebox step-through latency, from pre-drug baseline of three groups of rats (n=5 in each case) at several intervals (0.5, 3 or 6 hr) after an intrathecal injection of 30 μg of morphine. B: Tail flick latency of the same rats.

The Effect of Chronic Morphine Administration on Locomotion, Nociception and Placement Conditioning

Activity. The previous experiments indicated that motor activity was not altered after a single ITH morphine injection. It was possible, however, that overt behavioral changes might be more likely to develop as a consequence of chronic spinal administration. Therefore the next study examined the influence of repeated ITH injections of 30 μg of morphine on step-through latency and on tail flick. In this experiment, animals were assigned to either a morphine or a saline group in a counterbalanced order on the basis of their pre-drug baseline step-through trial. Immediately after this trial they received an ITH injection of either morphine (30 μg) or saline. A second injection was given on the next day, a third on the following day and a fourth injection on the subsequent and last day of the study. Approximately 35 min after the second, third and fourth injections, step-through latencies were determined for all animals. The mean of these three measurements was calculated for each rat. In addition to the step-through latencies, TF latencies were obtained from each rat on the last experimental day, i.e., after the fourth injection. The results of this experiment are shown in Fig. 4. On the left side of the figure is the median ST score for each of the two groups; on the right side of the figure are the TF scores for the same subjects. As indicated, the ST latencies of morphine animals (n=6) were significantly lower than the corresponding latencies of the saline animals (n=4), ($U=1$, $p<0.02$). During the course of the chronic daily injections saline animals became less active and engaged in other, nonlocomotor activity, such as grooming. In contrast, morphine injected animals remained active and continued to move across the shuttlebox over successive days.

In addition to the locomotor differences between the two groups, there was also a significant difference on the TF test ($U=0$, $p<0.01$). This result, shown on the right side of Fig. 4, indicates that the analgesic efficacy of ITH morphine was maintained for at least four injections.

Finally, in this experiment there was once again a perfect correlation between the TF scores of the saline animals and their ST latencies on the same day, i.e., after the fourth injection. Even with only four rats in the saline group, the relationship was "statistical," $r_s=1.0$, $p<0.05$.

Place conditioning. In the place conditioning experiments the five preconditioning preexposures to the shuttlebox provided a means of determining whether the rats could in fact discriminate between the two shuttlebox compartments and whether any animal had a tendency either to stay on the side he was placed or to escape from the side he was placed on and stay in the alternate side. During the preexposure period every rat developed a preference for the chamber with the black rubber mat on the floor, regardless of whether he was placed on that side on any given day. Therefore all drug injections were paired with the initially non-preferred grid floor, whereas, on the test day all rats were placed on the previously preferred black rubber mat floor.

The results of the place conditioning test are summarized in Fig. 5. The total number of seconds spent in the previously nonpreferred compartment is shown as a function of systemic injections (left side of the figure) and intrathecal injections (right side of the figure). In each case, the saline injected animals (open bars) spent significantly less time in the drug compartment than the respective morphine injected animals (filled bars). For systemic administration; $U=2$, $n=5$ for saline and 6 for morphine, $p<0.01$; for intrathecal administration; $U=0$, $n=7$ for saline (with a range of 0–227 sec) and 5 for morphine (with a range of 445–581 sec), $p<0.001$.

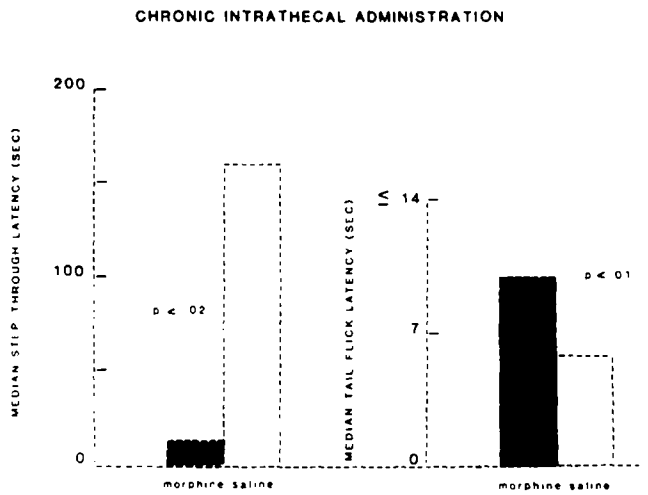

FIG. 4. Median step-through latency (left side) and tail flick latency (right side) of two groups of rats. One group (open bars) received four intrathecal injections of saline (n=4), the other group (filled bars) received four intrathecal injections of morphine (30 μg, n=6).

In each of the two experiments, therefore, those rats who received morphine, whether systemically or spinally, in the initially nonpreferred chamber, subsequently came to choose that side when the drug was withheld.

The fact that intrathecal morphine supported a place preference suggests that chronic spinal morphine, like systemic morphine, is positively reinforcing. An alternate interpretation, however, could be that the chronic spinal saline injections were aversive, and that the morphine effects simply reflect an opiate antagonism of nociceptive stimulation produced by chronic spinal injections.

It should be pointed out that during the daily injections there was no overt sign of any distress in the animals. The rats did not become irritable and did not resist handling or injection. Indeed, if such changes had occurred it would have been very difficult to continue with the injections as the animals were only minimally restrained and could move around freely.

Nevertheless, it was conceivable that repeated saline injections might have strengthened an aversion to that chamber that was already not preferred by the subjects. One way to obtain some indication of this was to compare the score of each rat on the final post-drug trial (on the mat) with his last comparable pre-drug trial (on the mat). This comparison would indicate whether the saline animals showed an increased aversion to the nonpreferred side after chronic injections. When the difference between these pre- and post-drug tests were calculated, it was found that, of the seven saline rats, two did in fact increase their avoidance of the nonpreferred chamber by 104 and 271 seconds, one rat showed no change, and the other four actually spent more time on that side after the injections (7, 26, 130 and 263 more seconds, respectively). As a group, the control rats did not show a consistent aversion for the side paired with saline.

In contrast, all five morphine rats increased the number of seconds they spent on the previously nonpreferred side by 356, 445, 478, 496 and 517 more seconds. This means that they actively chose to cross over from the side they had previously preferred (and on which they were placed) and stay on the side they had previously not chosen. If, in fact, morphine had simply acted to block some noxious stimulation from the injection, it would not be expected that they would actively seek the injection chamber, particularly during a period when they did not receive the drug. It is more likely that they would as a group show no preference for either chamber. These data are more consistent with the hypothesis that chronic intrathecal injections produced a positively reinforcing state, rather than a neutral, painless condition.

Finally, in each of these two experiments the TF latencies of the respective saline and morphine groups determined immediately after the place conditioning tests, did not differ. This indicated that the analgesic effect of the last systemic and intrathecal morphine injection, given approximately 24 hours earlier, had dissipated prior to the test day.

DISCUSSION

The most significant finding of these experiments was the demonstration that chronic intrathecal morphine altered locomotor activity and produced a place preference in rats.

Activity. It had been noted in previous reports that the analgesic effect of an acute intrathecal morphine injection in rats was not associated with any overt signs of sedation [31]. This anecdotal observation was confirmed in the present experiments. No change in activity was seen for up to six hours after a single intrathecal injection, in contrast to the dose-related sedative effect of acute systemic injections.

The results of the chronic morphine injections however, showed a different pattern. During repeated trials the saline control animals showed an increase in latency over days, presumably as a function of familiarity with the shuttlebox apparatus. This effect has previously been noted in other, unpublished experiments. That is, in several preliminary studies, using the same shuttleboxes, it has been observed that even unoperated, untreated rats show a decrease in exploratory activity with chronic exposure. Essentially, the rats habituate to the chambers. In contrast, the morphine injected animals continued to ambulate rapidly through the chambers. In some cases, it was noted that the morphine injected rats were also hyperactive in their cages after their injection, prior to step-through latency assessment. In effect, the behavior of the morphine injected rats was reminiscent of the enhanced activity that is sometimes elicited by a low dose of systemic morphine.

Place conditioning. The successful demonstration of place conditioning after systemic morphine is consistent with all previous studies. The finding that a profound place preference was engendered by intrathecal morphine represents the first report in any species that spinal opiates may provide a positively reinforcing drug cue.

Other alternatives for the place conditioning do not adequately explain these data. For example, all animals, whether injected with saline or morphine were exposed to each of the two shuttlebox compartments both before and during their drug treatments. Therefore, the experimental context was familiar to all animals. This fact argues against the possibility that morphine injected rats spent more time in the previously nonpreferred chamber because they were unfamiliar with the compartment and were exploring a "novel" environment.

The possibility that the morphine rats might have shifted their preference because they were hyperactive is also not a satisfactory explanation. First, the fact that hyperactivity

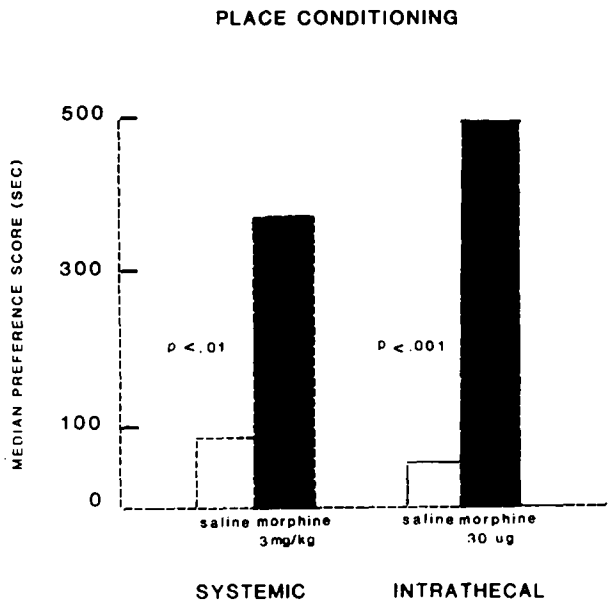

FIG. 5. Preference score: The median amount of time spent on the side of the test box that was previously paired with saline (open bars) or morphine (filled bars). The left side indicates the preference of rats who received four SC injections of either saline (n=5) or 3 mg/kg of morphine (n=6); the right side indicates the preference of rats who received four ITH injections of saline (n=7) or 30 μg of morphine (n=5).

was evident during administration (when analgesia was also obtained) does not necessarily mean that hyperactivity was also present 24 hr after the last drug injection (when analgesia was no longer detected). Second, even if the animals were hyperactive on the day after their last injection there is no reason to assume that activity per se would preclude or interfere with a valid place preference. It should be emphasized that the morphine animals spent nearly the whole test period in the previously nonpreferred, drug related chamber (i.e., 445 to 581 sec out of 600 sec). This observation is not compatible with the suggestion that the animals were shuttling back and forth across the chambers.

Interestingly, the parallel observation of place conditioning and hyperactivity is similar to the recent report of van der Kooy *et al.* who found that the specific brain sites which supported conditioning after morphine microinjection also elicited hyperactivity [27].

The conclusion proposed here is that the behavioral changes in activity and preference produced by chronic spinal morphine reflect a direct supraspinal locus of action. An alternative interpretation however, would be that such effects were mediated directly by the spinal cord. It is true that spinal reflexes can be directly influenced by the local application of opiates. For example, after spinal transection, the defensive tail flick reflex is still responsive to systemic morphine [11]. Furthermore, during opiate withdrawal characteristic abstinence signs are seen even in chronic spinal preparations [29]. Presumably, however in intact animals, such as those in the present study, any sensory disturbances originating at the site of the spinal infusion must reach supraspinal levels for the consequences to be expressed. The possibility that chronic spinal saline infusions might have been aversive has already been addressed. This suggestion does not appear to be a sufficient explanation for the profound difference between the morphine and saline groups. Perhaps however, the analgesic effect of morphine infusion produced some sort of disruption in spinal nociceptive transmission that was perceived supraspinally even in the absence of exogenous noxious stimulation. The perception of such a sensory disturbance might serve as a positively reinforcing cue. Translated to the clinical situation, the relief of chronic pain itself might be rewarding regardless of whether or not a direct euphoric effect is elicited by spinal opiates. Such issues, of course may also be a factor in the conditioning produced by systemic or other routes of morphine administration.

Why weren't any supraspinal consequences of intrathecal morphine appreciated in previous animal research? First, most observations concerning the side effects of spinal opiates in animals were confined to the first 60 minutes after a single injection. Many of the untoward reactions reported in the clinical literature, particularly after ITH injection, occurred several hours after one or more injections. Second, it should be noted that most animal studies used doses that were much lower than that needed to produce equivalent analgesia by the systemic route. In contrast, most clinical trials used doses that were comparable to those normally given systemically (4–10 mg), doses which may have produced greater absolute amounts of opiate in the brain. A third point concerns the difference between the two routes used for spinal injection. Most drugs were injected intrathecally in animals and epidurally in humans. Because of the vascularity of the epidural compartment this route results in higher blood concentrations of opiate than the intrathecal route and perhaps a more rapid transit to the brain. In fact, even though he did not specifically determine whether the drug reached the brain via the blood stream or the cerebrospinal fluid, Yaksh reported that epidural injections in cats and monkeys also elicited side effects such as itching, retching and respiratory depression [30,32]. Fourth, animal experiments were limited to a single drug as opposed to a clinical combination of drugs, and fifth, the posture of the laboratory subjects did not promote rostral flow of the drug.

At present, no clinical reports of euphoria after acute spinal morphine have been published. This is suprising in view of the fact that the local concentration of opiates in the CSF after acute intrathecal administration is several orders of magnitude greater than that resulting from systemic injection [17] and, that such high concentrations are presumed to be responsible for the untoward side effect of respiratory depression.

In addition to numerous reports concerning acute administration however, several studies have shown that chronic, usually terminally ill cancer, pain patients obtain long lasting pain relief from chronic spinal opiate infusion [6, 20, 37]. Such patients, in contrast to acute pain patients, rarely complain of any opiate side effects, presumably because they have become tolerant as a result of prior systemic exposure. Tolerance may account for the absence of a euphoric reaction in this population. However such reactions might have relevance for the application of the intrathecal technique to chronic, non-malignant pain patients. Further examination of this phenomenon should increase our understanding of the anatomical and physiological substrates of acute and chronic opiate effects as well as the nature of positive reinforcement in general.

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