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Central Administration of Prostaglandin E_2 Facilitates While $F_{2\alpha}$ Attenuates Acute Dependence Upon Morphine Rats[1]

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NIELSEN, J. A. AND S. B. SPARBER. *Central administration of prostaglandin E_2 facilitates while $F_{2\alpha}$ attenuates acute dependence upon morphine in rats.* PHARMACOL BIOCHEM BEHAV 22(6) 933–939, 1985.—The effects of prostaglandin D_2 (PGD_2), E_2 (PGE_2), and $F_{2\alpha}$ ($PGF_{2\alpha}$) on acute dependence on morphine were investigated. Five mature, male Long-Evans rats were trained to lever press for food reinforcement on a fixed-ratio 30 schedule (FR 30 behavior) and implanted with permanent guide cannulas with the tips of the cannulas in their right lateral brain ventricles. The experimental protocol began with a 45 minute behavioral session and brain infusion (1 μl/minute of a solution containing 2.3 mM $CaCl_2$ in 0.9% saline, ICV). Fifteen minutes into the session the rats were injected with 7.5 mg morphine/kg (IP). Beginning 2.25 hours later the brain infusion was reinitiated during a second 45 minute behavioral session which was interrupted after 15 minutes to inject 1.0 mg naloxone/kg (IP). In several experiments a dose of PG, which did not in-and-of-itself affect behavior, was added to the infusion medium. Prior to the naloxone injection it was ascertained that the behavioral effects of morphine had dissipated. The injection of naloxone or saline did not alter behavior of the rats while they were being infused with a PG or PG vehicle. Injection of naloxone, 3 hours after the injection of morphine, resulted in a significant suppression of FR 30 behavior (withdrawal). A dose of PGE_2, which did not alter the initial suppressant action of morphine, potentiated the naloxone effect. A dose of $PGF_{2\alpha}$, which likewise did not alter the initial action of morphine, antagonized the naloxone effect. However, a higher dose of $PGF_{2\alpha}$ which enhanced the initial morphine effect, caused an enhanced naloxone effect as well. PGD_2 did not alter the actions of morphine or naloxone. It is concluded that infusion of various PGs into the brains of rats differentially alters their responsiveness to morphine and dependence upon the opiate. It is further concluded that the dose and initial interactive effect of PGs and morphine are important determinants of the direction and degree of the expression of withdrawal.

Prostaglandins Morphine Dependence Operant behavior Naloxone Rats

IN the accompanying paper we suggest that prostaglandins (PGs) may be important in acute tolerance to and dependence on morphine [12]. Others have suggested PGEs may affect the development and/or expression of dependence on morphine. Schulz and Herz [15] have shown that PGE_1 produced an effect similar to that of the opiate antagonist naloxone in the *in vitro* myenteric plexus, longitudinal muscle strip preparation from guinea pigs tolerant to and dependent on morphine. In addition, increased sensitivity to PGE's effects develops after morphine treatment. Traber and coworkers [19] found the PGE_1-induced cyclic adenosine monophosphate formation was enhanced in morphine-treated neuroblastoma × glioma hybrid cells. Weeks and Collins [21] found that PGE_1, in doses which had no effect in morphine-free rats, caused what they described as depression in morphine-dependent rats. More recently, Ramirez-Solares and coworkers [14] have shown that PGE_1 and PGE_2 potentiated naloxone-induced contractions in the guinea pig ileum continuously exposed to morphine. $PGF_{2\alpha}$ had no effect in this regard. Ramirez-Solares and colleagues suggested that PGEs participate in the expression of physical dependence upon morphine, but not in the development of this phenomenon.

There is much more PGD_2 and $PGF_{2\alpha}$ than PGE_2 in the CNS of the rat [1,18]. However, no one has implicated PGD_2 or $PGF_{2\alpha}$ in the acute actions of and the development of dependence on morphine. Therefore, in addition to the infusion of PGE_2, PGD_2 and $PGF_{2\alpha}$ were infused into the CNS to see if they too would alter the initial action of morphine and the effects of naloxone in morphine-treated rats.

METHOD

Drugs

Morphine sulfate (S. B. Penick Company, New York, NY) and naloxone hydrochloride (generously provided by Endo Laboratories, Garden City, NY) were dissolved in 0.9% saline. All injections were intraperitoneal (IP) in a volume of 1 ml/kg of body weight.

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TABLE 1
EXPERIMENTAL PROTOCOL

Time (min)	Event
0	Place rat in operant chamber. Start behavioral session and brain infusion (1 μl/min).
15	Give injection (morphine or 0.9% saline).
45	Stop behavioral session and brain infusion. Remove rat from operant chamber.
180	Place rat in operant chamber. Start behavioral session and brain infusion.
195	Give injection (naloxone or 0.9% saline).
225	Stop behavior session and brain infusion. Remove rat from operant chamber.

The medium for intracerebroventricular (ICV) infusions contained 2.3 mM $CaCl_2$ in 0.9% saline. PGD_2 was dissolved in ethanol and added to the infusion medium. The concentration of ethanol in the PGD_2 solutions was about 1%. PGE_2 and $PGF_{2\alpha}$ were dissolved in the infusion medium. Infusion was at a rate of 1 μl/minute. PGD_2, E_2, $F_{2\alpha}$ (generously provided by Dr. J. Pike, The Upjohn Company, Kalamazoo, MI) were stored in solid form at −20°C.

Drug concentrations (PGs) and doses [morphine (7.5 mg/kg) and naloxone (1.0 mg/kg)] are expressed in terms of their free acid or base. All drugs were prepared fresh daily.

Methods

Five drug-naive, mature (400–450 g), male Long-Evans rats (Simonsen, Gilroy, CA) were shaped to lever press on a fixed-ratio 30 (FR 30) schedule for food reinforcement as described previously [12].

The rats were implanted with infusion cannulas with cannula tips in their right lateral ventricles. The stereotaxic coordinates were A0.0, L1.6 [13]. The cannulas were made by modifying stainless steel infusion cannulas (D. A. Kopf, Tujunga, CA). Cannula construction and implantation are described in detail elsewhere [11].

The daily experimental protocol (Table 1) began 8 days after cannula implantation. At approximately the same time each morning the rat was placed in the operant chamber. A 45-min behavioral session and brain infusion were begun simultaneously. Fifteen minutes into the session the rat was removed and injected with morphine or a 0.9% saline solution. After the session the rat was returned to its home cage. One hundred and thirty-five minutes later this procedure was repeated, with the exception that naloxone or saline was injected. Three hours separated the two injections.

Prostaglandins and FR 30 Behavior

Our goal was to determine if PGD_2, PGE_2, or $PGF_{2\alpha}$ modified morphine's effect on FR 30 behavior or the effect of naloxone in morphine-treated rats. Initially, the rats were habituated to the infusion and injection procedure by exposing them to PG vehicle (infusion medium) and saline. Within 14 days their behavior was stabilized, evidenced as a coefficient of variability of 15% or less for the last 3 days of the 14 day period. Then it was ascertained that 1 mg naloxone/kg was devoid of behavioral effects. The effects of various doses of PGD_2, (0.25, 0.5 and 1.0 μg/μl/min, ICV) PGE_2, (0.1 and 0.2 μg/μl/min, ICV) and $PGF_{2\alpha}$ (0.5 and 1.0 μg/μl/min, ICV) were determined. $PGF_{2\alpha}$ was infused (ICV) twice during the first week, with 2 days separating experiments. Two doses of PGE_2 were administered the second week, while the 3 doses of PGD_2 were infused the third and fourth weeks. Control sessions were comprised of the last 3 days of the 14 day habituation period and 3 sessions performed on days when PGs were not infused. No significant baseline shift was observed, the subjects performing within±1 S.D. of their initial (3 day) control rates throughout these experiments. After establishing which doses of the various PGs were behaviorally inactive, they were infused, on 3 separate occasions, in order to verify that a combination of PGs and 1 mg naloxone/kg was likewise inactive in this regard.

Morphine Experiments

Morphine experiments were started one week after the PG experiments described above. Rats were administered morphine every Friday for 5 weeks to determine if a behaviorally inactive dose of naloxone would disrupt behavior in morphine-treated rats and if behaviorally inactive doses of PGD_2 (0.25 μg/min), PGE_2 (0.1 μg/min), or $PGF_{2\alpha}$ (0.25 and 0.5 μg/min) would potentiate or attenuate morphine's acute effect on behavior or naloxone-induced suppression of behavior in morphine-treated rats. Control sessions were performed each Tuesday and Thursday. Two doses of $PGF_{2\alpha}$ were used because the higher dose augmented the initial suppressant effect of morphine on behavior, and we wanted to see if a lower dose would be devoid of this action and yet alter naloxone's effect.

Three of the 5 rats were infused with the vehicle solution and the other 2 rats with a solution containing PGE_2 (0.1 μg/min) on week 1. All rats were injected with morphine (7.5 mg/kg), followed 3 hours later by naloxone (1 mg/kg). Four weeks later (week 5) the rats were injected with morphine and naloxone as usual. The 2 rats which had initially been infused with a solution containing PGE_2 were infused with the vehicle solution, while the other 3 rats were infused with a solution containing PGE_2 (0.1 μg/min). In this manner we could gain information about whether changes in response to PGE_2, morphine or naloxone were occurring during the course of experimentation.

During the 3 weeks separating the two phases of the PGE_2-morphine experiments (weeks 2–4), all rats were infused once a week with a solution containing other PGs and injected with morphine and naloxone. The infusion solutions for the 3 weeks included $PGF_{2\alpha}$ (0.5 μg/min), PGD_2 (0.25 μg/min), and $PGF_{2\alpha}$ (0.25 μg/min), respectively. This allowed us to determine if these PGs modified morphine's acute effect of FR 30 behavior and the behavioral suppressant effect of naloxone in morphine-treated rats.

Wednesday of week 3 all the rats were infused with the vehicle solution and injected with saline, followed 3 hours later by naloxone. This experiment allowed us to determine if the rats were residually dependent on morphine 5 days after administration of 7.5 mg morphine/kg.

Data Analysis

Data from the experiments where a PG was administered, but no morphine was injected, were expressed as a percentage of the average behavior, during the appropriate session, of the last 3 days prior to the beginning of the PG experi-

TABLE 2

EFFECTS OF $PGF_{2\alpha}$, PGE_2, AND PGD_2 ON MORPHINE-INDUCED SUPPRESSION OF BEHAVIOR*

Infusion (ICV)	Control FR 30 Behavior (responses/second)	Morphine (7.5 mg/kg, IP) (% of control)
Vehicle (1 μl/min)	1.37 ± 0.26	50 ± 21†
$PGF_{2\alpha}$ (0.25 μg/min)	1.35 ± 0.15	53 ± 26†
$PGF_{2\alpha}$ (0.5 μg/min)	1.37 ± 0.16	19 ± 31†‡
PGE_2 (0.1 μg/min)	1.27 ± 0.19	51 ± 22†
PGD_2 (0.25 μg/min)	1.33 ± 0.16	62 ± 19†

*Fifteen minutes into a 45-minute behavior/infusion session the rats (N=5) were injected with morphine. The vehicle infusion medium contained 2.3 mM $CaCl_2$ in a 0.9% saline solution. Control behavior was determined the day before each experiment. All values are expressed as the mean ± 1 S.D.

†$p<0.05$ compared with vehicle infusion and vehicle injection (2-tailed, paired Student t-test).

‡$p<0.05$ compared with vehicle infusion and morphine injection (2-tailed, paired Student t-test).

TABLE 3

EFFECTS OF $PGF_{2\alpha}$, PGE_2, AND PGD_2 ON NALOXONE-INDUCED SUPPRESSION OF BEHAVIOR IN MORPHINE-TREATED RATS*

Infusion (ICV)	Control FR 30 Behavior (response/second)	Naloxone (1 mg/kg, IP) (% of control)
Vehicle (1 μl/min)	1.46 ± 0.12	66 ± 20†
$PGF_{2\alpha}$ (0.25 μg/min)	1.49 ± 0.10	87 ± 23‡
$PGF_{2\alpha}$ (0.5 μg/min)	1.48 ± 0.21	6 ± 2†‡
PGE_2 (0.1 μg/min)	1.40 ± 0.12	45 ± 21†‡
PGD_2 (0.25 μg/min)	1.54 ± 0.17	65 ± 20†

*Fifteen minutes into a 45-minute behavior/infusion session the rats (N=5) were injected with morphine (7.5 mg/kg, IP). One-hundred thirty-five minutes after the end of the session this procedure was repeated, with the exception that naloxone was injected. The vehicle infusion medium contained 2.3 mM $CaCl_2$ in a 0.9% saline solution. Control behavior was determined the day before each experiment. All values are expressed as mean ± 1 S.D.

†$p<0.05$ compared with vehicle infusion and vehicle injection (2-tailed, paired Student t-test).

‡$p<0.05$ compared with vehicle infusion and naloxone injection (2-tailed, paired Student t-test).

ments. Data from the morphine experiments, where morphine and naloxone were injected, were expressed as a percentage of the behavior during the appropriate session of the last control performed that week. All data were analyzed by a paired Student t-test, with each rat serving as its own control [17].

RESULTS

The rate of lever pressing for all rats during the last 3 days prior to initiating drug experiments was 1.57±0.34 and 1.41±0.16 responses per second for the two 15 minute sessions before injection, and 1.43±0.15 and 1.48±0.21 responses per second for the two 30 minute sessions after injection. Control response rates did not change appreciably throughout the course of experimentation. For example, behavior the day before each of the 5 morphine and naloxone injections was within±1 S.D. of the rats initial 3 day control behavior (Tables 2 and 3). In addition, naloxone had no effect on behavior except when administered after morphine (see below).

Prostaglandins and FR 30 Behavior

$PGF_{2\alpha}$, PGE_2, and PGD_2 significantly suppressed behavior (Fig. 1). $PGF_{2\alpha}$ (1 μg/min) had no effect during the first 15 minutes, but began to suppress behavior during the last 30 minutes of the session (Fig. 2). A lower dose of $PGF_{2\alpha}$ (0.5 μg/min) had no effect on behavior during the 45 minute session (Figs. 1 and 2) or a 45 minute session performed 3 hours later. In a similar manner, PGE_2 (0.2 μg/min) began to de-

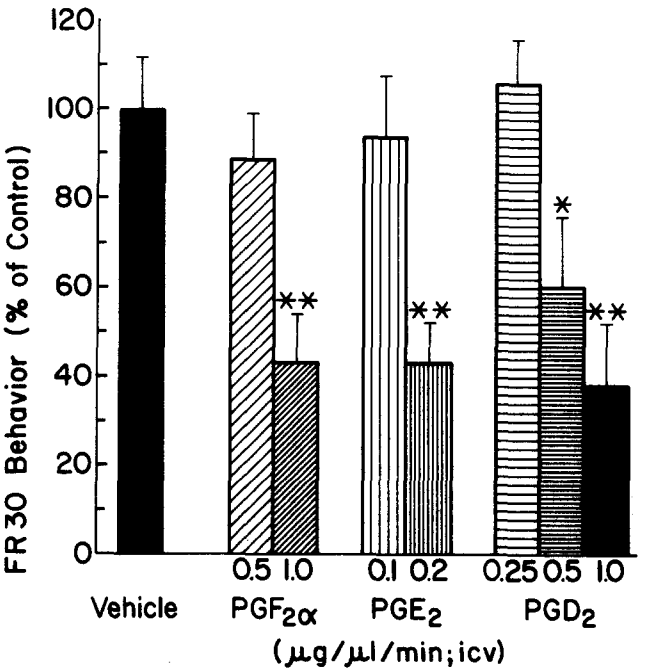

FIG. 1. $PGF_{2\alpha}$, PGE_2, and PGD_2 suppressed FR 30 behavior in rats. The rats (N=5) were infused during a 45-minute behavioral session which was interrupted at 15 minutes for an injection of saline. Data shown here were from the last 30 minutes of the session. All values are expressed as the mean±1 S.D. *$p<0.05$, **$p<0.01$ compared with vehicle infusion (2-tailed, paired Student t-test).

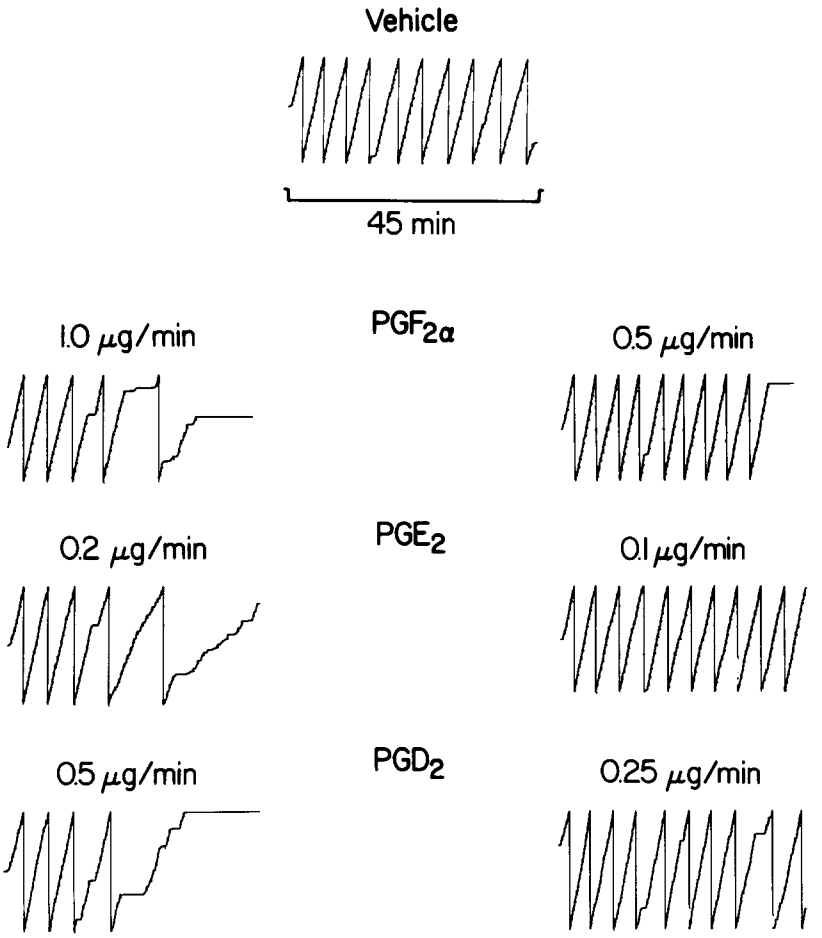

FIG. 2. Sample cumulative records of FR 30 behavior for rat 49 showing effects of active and inactive doses of $PGF_{2\alpha}$, PGE_2, and PGD_2. Vehicle or solutions of various PGs were infused into the rat's lateral ventricle at a rate of 1 μl/min during the 45-minute behavior session. The vehicle solution contained 2.3 mM $CaCl_2$ in 0.9% saline. Responding rate is reflected by slope of the recording. Delivery of a reinforcer is indicated by a pip of the record.

press behavior during the last 30 minutes of the 45 minute session, while a lower dose (0.1 μg/min) had no effect on behavior during the 45 minute sessions. PGD_2 (0.5 and 1.0 μg/min) suppressed behavior, while a lower dose (0.25 μg/min) was devoid of this effect during any of the times tested. Infusion of a solution containing a behaviorally inactive dose of PGD_2 (0.2 μg/min), PGE_2 (0.1 μg/min) or $PGF_{2\alpha}$ (0.5 μg/min) during the two 45 minute sessions and injection of saline during the first 45 minute session, and a behaviorally inactive dose of naloxone (1 mg/kg) during the second 45 minute session, also had no effect on behavior.

Morphine Experiment

Morphine (7.5 mg/kg, IP) significantly suppressed behavior (Table 2). Three hours later the rats had recovered from the behavioral suppressant effects of morphine. Naloxone, administered at this time, significantly suppressed behavior (Table 3), indicating evidence of acute dependence. Infusion of a solution containing the higher dose of $PGF_{2\alpha}$ (0.5 μg/min), significantly potentiated the initial effects of morphine. Three hours later, when the rats had recovered from this effect, $PGF_{2\alpha}$ (0.5 μg/min) also potentiated the effects of naloxone. Infusion of a solution containing a low dose of $PGF_{2\alpha}$ (0.25 μg/min) which had no effect on morphine-induced suppression of behavior, or behavior 2.75 to 3 hours after morphine, however, caused a significant reduction in the extent to which naloxone suppressed behavior. PGE_2 (0.1 μg/min) did not alter the initial effect of morphine upon behavior. Additionally, behavior was at control rates 2.75 to 3 hours after coadministration of PGE_2 and morphine. However, when naloxone was injected after the PGE_2-morphine combination, a significant augmentation of naloxone's effect was observed. Infusion of a solution containing PGD_2 (0.25 μg/min) had no effect on the morphine-induced suppression of behavior, behavior 2.75 to 3 hours after morphine, or naloxone's effect.

Figure 3 shows cumulative records depicting naloxone-induced suppression of behavior in morphine-treated rats and the attenuation and potentiation of this effect by $PGF_{2\alpha}$ (0.25 μg/min) and PGE_2 (0.1 μg/min), respectively.

We were not able to detect evidence for the development

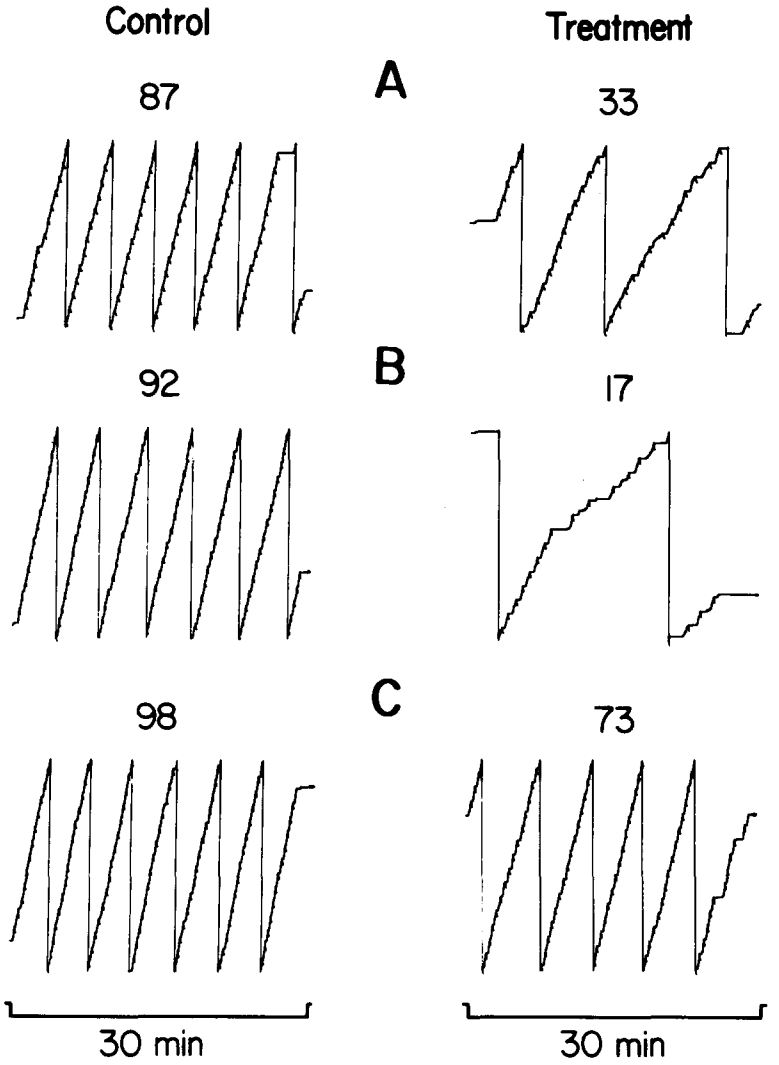

FIG. 3. Sample cumulative records of FR 30 behavior for rat 49 showing that naloxone suppressed behavior after morphine pretreatment. PGE_2 (0.1 μg/min) and $PGF_{2\alpha}$ (0.25 μg/min) potentiated and attenuated, respectively, this effect of naloxone. The rat was injected fifteen minutes into a 45-minute behavior session with morphine (7.5 mg/kg, IP). During this time, vehicle or solutions of various PGs were infused (ICV) at a rate of 1 μl/min. One hundred thirty-five minutes later this procedure was repeated except that naloxone (1.0 mg/kg, IP) was injected. Responding shown here was emitted during the 30-minute session after the last injection. Controls involved infusion of the vehicle (2.3 mM $CaCl_2$ in 0.9% saline) and injection of saline twice and were performed the day before the experiments. The experiments involved the infusion of the vehicle to which nothing (panel A), PGE_2 (0.1 μg/min) (panel B), or $PGF_{2\alpha}$ (0.25 μg/min) (panel C) was added and injection of morphine (7.5 mg/kg) followed 3 hours later by naloxone (1 mg/kg). The numbers above the records indicate the number of reinforcers earned by the animal.

of tolerance to morphine's behavioral suppressant effect when morphine was administered every 7 days. When the vehicle solution was infused and morphine was first administered, behavior was suppressed to 59% of control (3 rats). When the vehicle solution was infused and morphine was administered after 5 weekly injections of morphine, behavior was suppressed to 56% of control (2 rats).

The rats were apparently not dependent on morphine 5 days after its administration. A dose of naloxone (1 mg/kg), which affected rats 3 hours after morphine, had no effect if it was administered 5 days after the last of 4 weekly injections of morphine. This suggested that the rats were dependent on morphine 3 hours, but not 5 days after injection.

The effect of naloxone was not changed by weekly injections of morphine. When the vehicle was infused and naloxone was administered 3 hours after morphine was first administered, behavior was suppressed to 69% of control. When the vehicle was infused and naloxone was adminis-

tered 3 hours after the fifth weekly injection of morphine, behavior was suppressed to 63% of control.

The effect of PGE_2 on naloxone-induced suppression of behavior in morphine-pretreated rats was not apparently altered by weekly injections of morphine. When a solution containing PGE_2 (0.1 μg/min) was infused and naloxone was administered 3 hours after the first administration of morphine, behavior was suppressed to 38% of control (2 rats). When a solution containing PGE_2 (0.1 μg/min) was infused and naloxone was administered 3 hours after the fifth weekly administration of morphine, behavior was suppressed to 50% of control (3 rats).

DISCUSSION

This study shows that $PGF_{2\alpha}$ and PGE_2 alter the expression and/or development of dependence on morphine. It has been suggested that the development of increased sensitivity to PGE stimulation of adenylate cyclase may be regarded as a process of adaptation to the presence of opiates [5]. Others have found increased sensitivity to PGEs in morphine-treated preparations [15, 19, 21]. The signs which occur when the opiate is withdrawn or an opiate antagonist is administered could represent an expression of the supersensitivity to the PGEs. If such is the case, PGEs should potentiate opiate withdrawal signs. It was found that PGE_2, in a dose which had no effect on morphine-induced suppression of behavior, potentiated the naloxone-induced behavioral suppression (withdrawal) in morphine-treated rats. In a similar manner, PGE_1 and PGE_2 potentiated naloxone-induced contractions in the guinea pig ileum continuously exposed to morphine [14].

Hammond and coworkers [8] claimed that PGE_2 inhibited the induction of morphine tolerance/dependence in the guinea pig ileum. However, this effect of PGE_2 was very small and was seen at a dose of PGE_2 sixty-six times that which reversed morphine-induced inhibition of electrically-evoked contractions in the guinea pig ileum. It is likely that PGE_2 decreased the initial effect of morphine, which led to less tolerance or dependence on morphine upon subsequent challenge.

$PGF_{2\alpha}$ has previously been suggested to have no effect on the development of dependence on morphine [14]. However, in the present study it was shown that $PGF_{2\alpha}$, in a dose which had no effect on morphine-induced suppression of behavior, antagonized naloxone-induced behavioral suppression in morphine-treated rats. On the other hand, a dose of $PGF_{2\alpha}$ which potentiated morphine-induced suppression of behavior, potentiated the effects of naloxone in morphine-treated rats. This observation may be due to $PGF_{2\alpha}$ potentiating morphine's initial pharmacological effect. For example, increasing the dose of morphine pretreatment increased naloxone efficacy [16, 20, 22]. $PGF_{2\alpha}$ potentiation of morphine-induced suppression of behavior may be thought of as being functionally comparable to increasing the initial dose of morphine.

Horrobin [9] has stated "some PGs may have effects at low concentrations which disappear or even reverse at higher concentrations." For example, PGE_2 affects human red cell deformability at 10^{-11} M, is maximal at 10^{-10} M, and disappears at 10^{-9} M [3]. In addition, the effects of PGE_1 and PGA_2 in potentiating responses to noradrenaline in a perfused rat mesenteric vascular preparation was detected at 10^{-12} M, maximal at 10^{-11} M, and disappeared or reversed at 10^{-7} to 10^{-8} M [10]. Finally, $PGF_{2\alpha}$ promoted prolactin secretion by cultured rat pituitary cells at 10^{-10} M, is maximal at 10^{-8} M and disappears at 10^{-6} M [7]. Our data also support this concept in that a low dose of $PGF_{2\alpha}$ attenuated while a high dose potentiated naloxone-induced suppression of behavior in morphine-treated rats.

Collier and coworkers [5] have suggested that naloxone precipitates withdrawal in morphine-treated animals partially by stimulating PGE synthesis. This would suggest that indomethacin should antagonize the actions of naloxone, since indomethacin inhibits the synthesis of PGE. However, we found that indomethacin potentiated the effects of naloxone in morphine-treated rats [12]. We would like to suggest that it is not the *absolute amount* of PGE in the CNS that is important during the naloxone-induced withdrawal in morphine-dependent rats, but the *ratio* of PGs, perhaps PGE_2 to $PGF_{2\alpha}$, and that naloxone's effects during opiate dependence are increased by raising the $PGE_2/PGF_{2\alpha}$ ratio and decreased by lowering this ratio. Support for this suggestion comes from the finding that indomethacin decreases the amount of PGE_2 and increases the ratio of $PGE_2/PGF_{2\alpha}$ in rat brain [2,6], and this drug potentiates the effects of naloxone in opiate-dependent rats [12]. Furthermore, increasing the ratio of $PGE_2/PGF_{2\alpha}$ in rat brain by infusing PGE_2 into the ventricles led to a greater effect of naloxone in opiate-dependent rats (the present study). Finally, decreasing the ratio, by infusing $PGF_{2\alpha}$ intracerebroventricularly, led to a lesser effect of naloxone in opiate-dependent rats.

PGD_2 (a lipid structurally similar to PGE_2 and $PGF_{2\alpha}$, and administered at an approximately equimolar dose) had no effect on the behavioral suppressant action of morphine or the behavioral suppressant action of naloxone in morphine-treated rats. Therefore, the effects of PGE_2 and $PGF_{2\alpha}$ on naloxone's effect were not due to a nonspecific lipid effect. Furthermore, the morphine-naloxone combination did not merely increase the rats responsiveness to PG. If that were the case, then the PGs should have suppressed behavior after naloxone administration since high doses of the PGs decreased behavior. However, the naloxone-induced decrease in behavior was attenuated by the low dose of $PGF_{2\alpha}$ and unaffected by PGD_2.

In summary, it was found that the effect of $PGF_{2\alpha}$ infusion on morphine's and naloxone's behavioral suppressant effects was dose-dependent. A low dose of $PGF_{2\alpha}$ had no effect on morphine's acute action, and antagonized naloxone-induced behavioral suppressant action. However, a higher dose of $PGF_{2\alpha}$ potentiated the behavioral suppressant action of both morphine and naloxone. On the other hand, PGE_2, in a dose which had no effect on the acute behavioral-suppressant action of morphine, potentiated naloxone-induced behavioral suppression in morphine-treated rats. It is concluded that the adaptive changes (dependence) associated with morphine are even more sensitive to PGs than the acute effects of morphine.

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