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PGD_2 Effects on Rodent Behavior and EEG Patterns in Cats

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LAYCHOCK, S. G., D. N. JOHNSON AND L. S. HARRIS. *PGD_2 effects on rodent behavior and EEG patterns in cats.* PHARMAC. BIOCHEM. BEHAV. 12(5) 747–754, 1980.—Prostaglandin (PG) D_2 was studied to determine the pharmacological effects of this PG on the central nervous system. PGD_2 (0.45–4.05 mg/kg) decreased spontaneous locomotor activity in rats by as much as 66% of control, however, the neuromuscular coordination of mice, treated at the same doses of PGD_2, was not impaired. PGD_2 (0.05–4.05 mg/kg) also increased pentobarbital sleeping time in mice from 42% to 238% of control, in a dose-related manner. PGD_2 did not prevent convulsions induced in response to electroshock or pentylenetetrazol. Cats monitored for EEG responses to PGD_2 infusion displayed variable sensitivity to different doses (16–3000 μg) of drug, however, the characteristic response to PGD_2 was the conversion from a uniform low voltage, fast wave pattern to high voltage, slow waves. Cats administered PGD_2 were sedated and sometimes catatonic, and displayed brief periods of hypotension, bradycardia, diarrhea, analgesia and hyperthermia at higher doses of the drug. Thus, PGD_2 possesses sedative properties in rodents and cats and may have a role in the central nervous system.

PGD_2 Spontaneous locomotor activity Sleeping time Neuromuscular coordination EEG Anticonvulsant Sedation

A PHYSIOLOGICAL role for prostaglandins (PGs) in the central nervous system has been suggested based upon the evidence that PGs are synthesized by the brain [1, 2, 14, 24, 25], and the levels of PGs in the brain increase upon stimulation by neurotransmitter substances [14,24]. The major cyclooxygenase products identified in slices, and homogenates, of brain from the rat, guinea-pig, rabbit and cat are PGD_2, $PGF_{2\alpha}$ and PGE_2 [1, 2, 24, 25], with PGD_2 found in the highest concentration in the brain of the rat and guinea-pig. PGs also have potent pharmacologic actions on the central nervous system with regard to enhanced release and turnover of certain neurotransmitters [8,20], and have pronounced behavioral effects [10]. Brain PGs have also been suggested as modulators of reproductive endocrine systems due to their actions in the hypothalamus and adenohypophysis [19]. PGs, especially of the E-type, have been repeatedly demonstrated to produce sedation in rodents [3, 6, 17, 22, 23], monkeys [5,17], and the cat [10,11]. Other observed responses to PGEs include anorexia [21], motor incoordination [22], inhibition of conditioned avoidance responses [17], and anesthesia [6]. PGs of the F-, A- and B-type, on the other hand, cause small or insignificant changes in behavioral tests [10, 14, 21]. In addition to overt behavioral responses, PGEs also affect electroencephalographic recordings such that amplitude is decreased [17], unsynchronized spontaneous discharge rate is decreased [5], and low voltage-high frequency recordings indicative of paradoxical sleep are increased [8].

Since PGD_2 has been reported to be the major PG synthesized in the brain of several species [1,2], this study was undertaken in order to define a possible physiological role for PGD_2 in the central nervous system. PGD_2 administered by the intravenous route to rodents and cats altered several parameters of behavioral pharmacology, including electroencephalogram (EEG) patterns. Since biological changes also accompany PG administration, possible correlations between changes in behavioral and biological parameters are discussed. In addition, the results are discussed with comparison to the reported effects of other PGs on the central nervous system.

METHOD

Female, albino mice (20–30 g) or Sprague-Dawley rats (130–260 g) were provided food and water ad lib before administration of test agents which were injected intravenously via the lateral tail vein (PGD_2) or intraperitoneally (pentylenetetrazol). Cats were USDA certified, fasted overnight prior to the day of experimentation, and were administered drug intravenously via a vein in the foreleg. Gallamine triethiodide was from Davis and Geck Pharmaceutical Co., pentobarbital sodium was from Abbott laboratories, pentylenetetrazol (Metrazol) was from Knoll Pharmaceutical Co. Prostaglandin D_2 was generously supplied by Upjohn Co. and was suspended in ethanol prior to dilution with 0.9% NaCl for injection (control animals received an equal percentage of ethanol alone in saline for injection).

Spontaneous Locomotor Activity (SLMA)

SLMA of rats injected intravenously with saline-ethanol (control) or PGD_2 in saline-ethanol was determined as interruptions of photocells in Woodard activity chambers.

Movement was measured cumulatively, beginning 5 min after injection, at 15 min intervals for 60 min. Three to five rats were used at each dosage level, with one animal per chamber.

Rotarod Performance in Mice

Groups of five animals were administered PGD_2 intravenously and 5 min later were placed upon a 5 rpm rotarod. The number of falls in 2 consecutive 5 min periods was recorded for each animal. Preliminary studies showed that no mouse fell more than once in 5 min; mice were considered uncoordinated or lacking in motivation if they fell more than twice in an experiment, not counting voluntary (side excursions) or reverse-rotational dismounts.

Pentobarbital Sleeping Time in Mice

Sodium pentobarbital (40 mg/kg) was administered intravenously alone or in combination with various concentrations of PGD_2. PGD_2 alone was also administered in this manner. The sleeping time for each animal was determined and defined as the time interval from initial loss of righting reflex to the time when the animal regained its righting reflex. Control animals received pentobarbital in saline containing an amount of ethanol equivalent to that used as a vehicle for PGD_2. The room temperature was maintained at 21–24°C.

Determination of Anticonvulsant Activity

Groups of five mice were injected intravenously with PGD_2 and 5 min later were treated with 34 mA of current (maximal electroshock) using paired ocular electrodes. Immediate display of tonic extension was evidence of convulsion. In other experiments, groups of five mice were injected intravenously with PGD_2 and 5 min later were administered pentylenetetrazol (120 mg/kg, IP). Control animals received an equivalent volume of saline-ethanol. Times to occurrence of tremors, clonic and tonic convulsions, and death were recorded.

EEG Studies in Acute Animals

Two cats were anesthetized with ether and cannulae placed in the trachea, a cephalic vein, and a femoral artery for artificial ventilation, drug administration, and blood pressure recording, respectively. Stainless steel screws were placed in the skull for monopolar EEG recordings, and needle electrodes served to obtain a lead II EKG. A rectal probe was used to monitor body temperature. Wound edges and pressure points were infiltrated with lidocaine containing norepinephrine, the ether removed, gallamine triethiodide injected, and artificial ventilation (10 ml room air/kg/3 sec) instituted. Sufficient time (minimum of 1 hr) was allowed for the effects of the general anesthetic to dissipate. PGD_2 was administered intravenously in increasing concentrations. One cat received 0.02–1.0 mg PGD_2 in 1 ml saline containing up to 0.4 g of ethanol every 20 min, and EEG-physiological recordings were collected at 10 min intervals. A second cat received 0.3, 0.9 and 300 mg PGD_2 at 1 hr intervals and EEG-physiological recordings were collected every 5 or 10 min. One hour after the final treatment with drug, the cat was administered ethanol in saline equivalent to the amount of ethanol in the highest concentration of PGD_2 in order to determine if the ethanol vehicle could reproduce the changes seen in response to PGD_2.

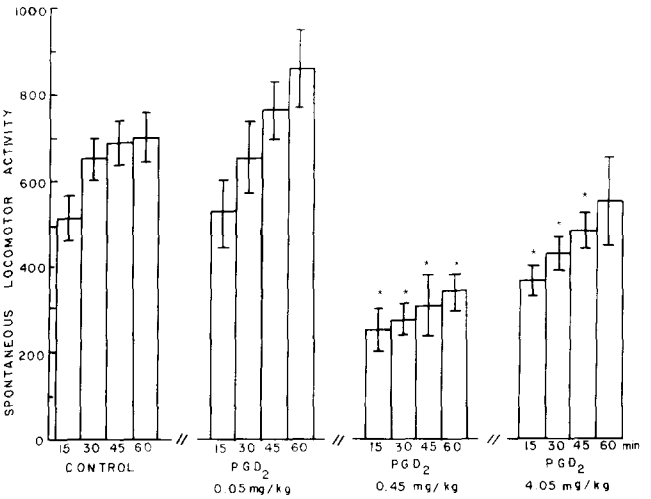

FIG. 1. Effects of PGD_2 on spontaneous locomotor activity (SLMA) in the rat. Animals were administered saline containing either 4% ethanol (control), or PGD_2 suspended in 4% ethanol, in the doses indicated, via intravenous injection. Bars represent cumulative mean (±SE) interruptions of photocells 15–60 min after placing each rat in a separate activity chamber. Asterisks (*) indicate SLMA value is significantly different ($p<0.05$) from control activity during the corresponding time interval, as determined using student's t test for unpaired values, n=8.

EEG Studies in Chronic Animals

Three cats weighing approximately 3 kg, previously prepared with chronically implanted cortical electrodes, were used for these studies. Animals had not received other drugs for several months prior to this study. Electrodes (1/4-in. stainless steel screws) were implanted through the skull so that the tips rested on the dura over the frontal, parietal, and occipital areas, bilaterally. A common electrode was placed in the bone over a frontal sinus.

Animals were accustomed to the observation cage for 1–2 hours before the start of each experiment, and were connected to the Grass electroencephalograph by means of a shielded cable that did not impair movement.

EEG recordings were obtained prior to each administration of drug to establish the normal pattern for each animal. Various concentrations of PGD_2 were administered intravenously in 0.5 ml of a saline-ethanol vehicle. EEG recordings were obtained periodically (approximately 2, 10, 20, 30, 40, 50, and 60 min and half-hour intervals thereafter) for up to 3 hours.

Statistical Analysis

Data collected during these studies were analyzed using Student's t test for unpaired data.

RESULTS

Effects of PGD_2 on Motor Activity, Barbiturate Sleeping Time and Convulsant Stimulation

PGD_2 decreased SLMA in rats injected intravenously with 0.45 and 4.05 mg/kg PGD_2 (Fig. 1). SLMA significantly decreased by as much as 42 and 66% of control values for the time period 15–30 min in animals treated with 0.45 and 4.05 mg/kg PGD_2, respectively. Both groups of animals treated

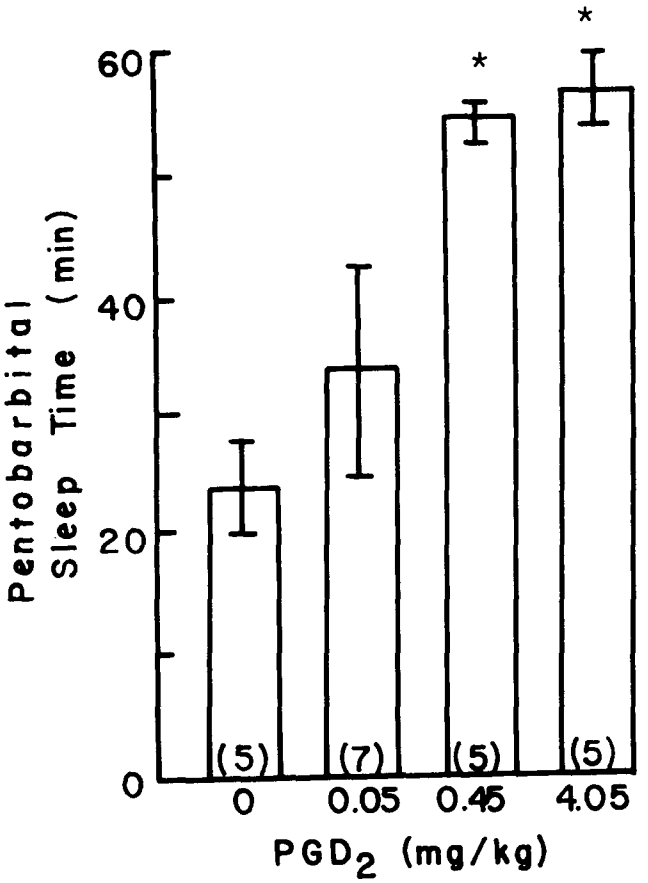

FIG. 2. Effects of intravenous PGD_2 administration on sodium pentobarbital-induced sleep time in mice. Pentobarbital (40 mg/kg) was administered intravenously with 1% ethanol (control) or PGD_2 dissolved in 1% ethanol, in the doses indicated. Asterisks (*) denote significantly different ($p<0.05$) sleep times (mean ± SE) for PGD_2-treated animals compared to control animals using student's t test for unpaired values. Numbers in parenthesis represent n for each group.

with 0.45 and 4.05 mg/kg PGD_2 had significantly less SLMA when compared to control values throughout 45 min of observation (Fig. 1), and the animals appeared sedated sitting in a crouched position for several minutes at a time with head lowered and eyes closed. The slightly greater activity level of rats treated with 4.05 mg PDG_2/kg than the different group treated with 0.45 mg/kg was not significant, and may be attributed to animal variation in size and inherent activity level. A lower dose of PDG_2 (0.05 mg/kg) did not decrease SLMA compared to control values during 60 min of observation, but rather SLMA was relatively constant throughout the 60 min of observation (Fig. 1).

Additional data revealing changes in central nervous system activity caused by PGD_2 were sought using the rotarod test of neuromuscular coordination. A rod rotating at 5 rpm did not cause control mice to fall more than once in 5 min, and 5 min after the injection of 0.05, 0.45, and 4.05 mg/kg PGD_2 (5 animals per dose) only one animal, injected with 0.45 mg/kg PGD_2, fell more than once (twice) during the observation intervals. Drug-treated mice did, however, appear sedated (sitting in one corner of the cage with head lowered) prior to placement on the rotarod, and displayed sluggish movement while on the rod. Mice, which were returned to the rotarod 30 min after treatment with PGD_2, did not fall during 5 min of testing. In one experiment, the speed of rotation of the rod was increased to 7 rpm, which was the maximum speed at which control animals were able to maintain their position without falling. At this faster speed, none of the mice treated with 4.05 mg/kg PGD_2 displayed motor incoordination or lack of motivation to remain on the rod.

Effects of PGD_2 upon the central nervous system were further evaluated by observing changes in pentobarbital sleeping time as well as drug-induced and electrically-stimulated convulsant behavior. Although 0.05 mg/kg PGD_2 caused a small but insignificant increase (42%) in pentobarbital sleeping time compared to control values (24 ± 4 min) in the absence of PGD_2, both 0.45 and 4.05 mg/kg PGD_2 significantly potentiated pentobarbital sleeping time by 229% and 238% of control, respectively (Fig. 2). When 1.35 mg/kg PGD_2 was administered with pentobarbital, the pentobarbital sleeping time was also significantly potentiated. However, mice treated with this concentration of PGD_2 alone did not lose their righting reflex although they appeared sedated, sitting in a crouch position for long periods; some animals displayed ataxia when prodded to change their position.

Intraperitoneal injection of pentylenetetrazol induced clonic and tonic convulsions in mice, followed by death, within several minutes. When PGD_2 (4.05 mg/kg) was administered intravenously to five mice 5 min prior to pentylenetetrazol, the animals showed tremors and clonic convulsions within 3 min, followed by tonic convulsions and death within 4–14 min after pentylenetetrazol. None of the animals treated with pentylenetetrazol, or pentylenetetrazol plus PGD_2, survived. In addition to pentylenetetrazol, central nervous system stimulation was induced by exposure of mice to electroshock. Five mice which were pretreated with PGD_2 (4.05 mg/kg) and 5 min later administered electroshock displayed an immediate tonic convulsion. Four of the five animals survived. In control animals, 80% recovered after electroshock treatment.

EEG Patterns, Blood Pressure and Heart Rate in Cats

Two cats (A and B) with acutely implanted EEG electrodes displayed variable sensitivity to PGD_2. Following the administration of 16 μg PGD_2 to cat A, the awake pattern of the EEG recording, characterized by uniform low voltage, fast waves, was converted after 3 min to periods of synchronized (high voltage, slow wave) activity interspersed with control-type activity (Fig. 3) suggestive of slow-wave sleep [13]. After reverting to the low voltage, fast record within 20 min, increasing the dose of PGD_2 to 60 μg in cat A caused the reappearance of slow waves 90–120 sec after drug administration. A slower than normal wave pattern was still seen 5 min post-drug; however, after 10 min the normal fast waves reappeared (data not shown). The EEG recordings of cat A administered 120 μg PGD_2 showed a marked decrease in amplitude within 10 sec, and between 30–50 sec a high voltage, slow wave form appeared (Fig. 3) which returned to the fast wave, lower voltage form after 1 min. When cat A was administered higher doses of PGD_2 (240, 480, 960 μg) at 20 min intervals, the EEG pattern was the same as that produced in response to 120 μg PGD_2. Pentobarbital administration, on the other hand, resulted in the appearance in the EEG of the characteristic high voltage, slow wave sleep pattern (Fig. 3).

The heart rate of cat A was 4 beats per second prior to administration of drug, and dropped to 3 beats per second

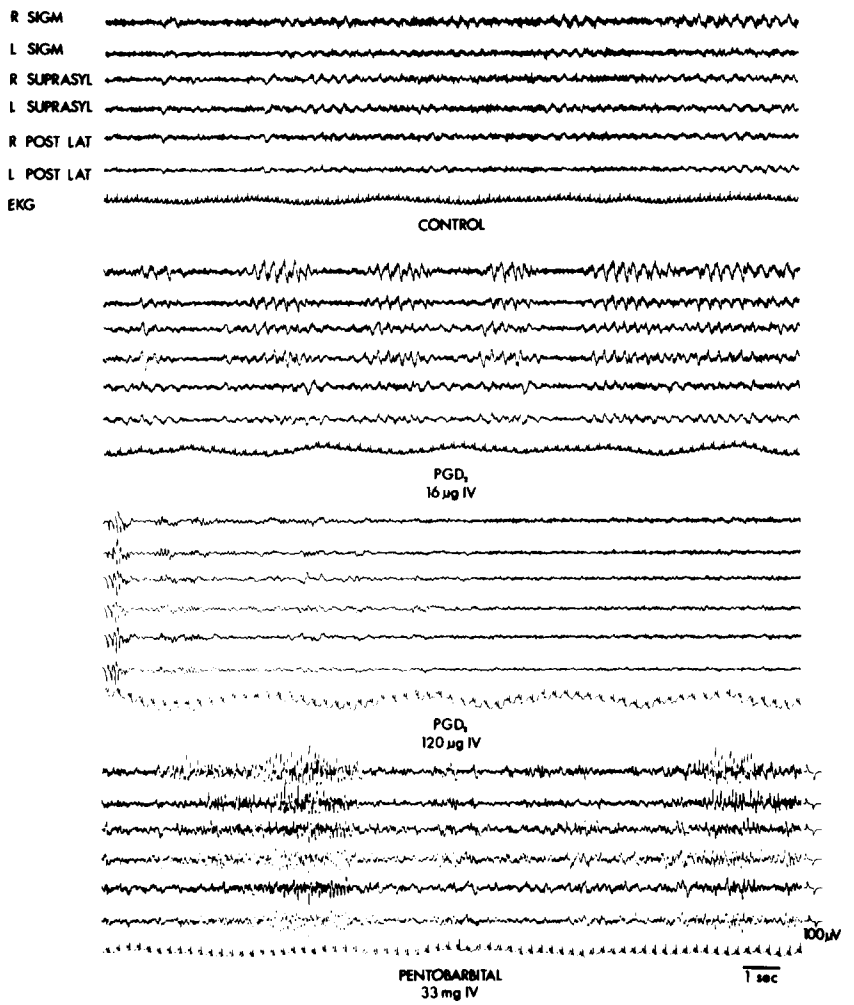

FIG. 3. Representative EEG recording of an acutely prepared, immobilized, artificially ventilated cat (A) before and after PGD_2 or pentobarbital administration. Time of recording after drug administration: PGD_2 (16 μg), 3 min; PGD_2 (120 μg), 30 sec; pentobarbital, 3 min. Abbreviations: sigmoid gyrus (SIGM); suprasylvian gyrus (SUPRASYL); posterior lateral gyrus (POST LAT); right (R); left (L); electrocardiogram (EKG).

after injection of 60, 120, 240, and 960 μg PGD_2; but, the normal rate was restored within 2–3 min after drug. The normal blood pressure reading for cat A was 140 mm Hg, and following the administration of 16, 40, 60, 120 and 240 μg PGD_2 in consecutive intravenous injections separated by 20 min intervals, blood pressure recordings decreased to 80, 55, 50, 40 and 40 mm Hg within 0.5–1.0 min, respectively, and returned to control pressures within 3–13 min after drug administration. Higher doses of PGD_2 (480 and 960 μg) lowered blood pressures to 40 and 55 mm Hg within 30 sec of administration, respectively, and recovery to a higher blood pressure was seen within 18 and 17 min, respectively.

The second cat (B) did not show any evidence of high voltage, slow waves on the EEG after administration of 300 or 900 μg PGD_2. However, following administration of 3 mg PGD_2 one hour after the 900 μg injection, high voltage, slow waves were noted within 60 sec of administration and by 3 min high voltage slow waves were prevalent in the EEG and were seen for at least 6 min (Fig. 4). During this period of slow-wave recording, the EEG was not altered during tactile stimulation; however, a pain stimulus (pinching of the toe pad) transiently converted the high voltage, slow waves to low voltage, fast waves. Ten minutes after administering 3 mg PGD_2 there was no longer any evidence of sustained high voltage, slow waves on the EEG.

Cat B also responded to PGD_2 (300 μg, 900 μg and 3 mg) with decreases in mean blood pressure from a control reading of 150 mm Hg to 75, 45, and 50 mm Hg, respectively, within one minute after injection, and recovered to near-control values after 14 min, except after 3 mg PGD_2 when blood pressure remained depressed for 50 min. In addition, 10 min after administering 3 mg PGD_2, the cat's body temperature rose from 32.5°C to 32.9°C. When an amount of ethanol (240 mg) equivalent to that injected with 3 mg PGD_2 was injected with saline vehicle as a control, the blood pressure fell from 115 mm Hg to 60 mm Hg within one minute, followed by a rapid increase to 100 mm Hg within 4 min and complete recovery to 115 mm Hg by 8 min after ethanol

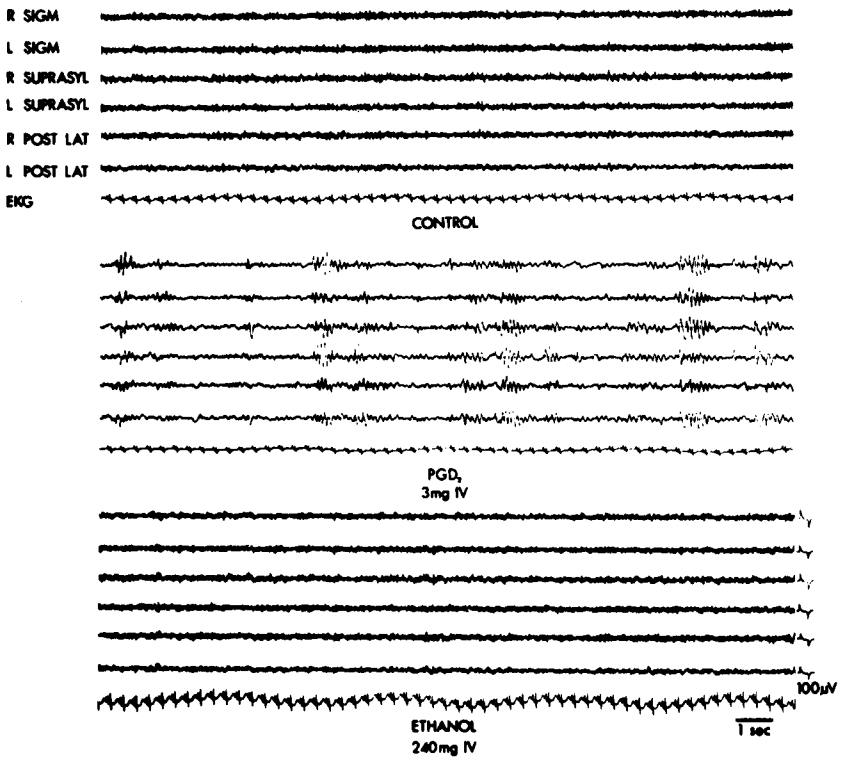

FIG. 4. Comparative effects of PGD_2 and ethanol on the EEG recording of an acutely prepared cat (B). EEG recordings 5 min after drug administration. See Fig. 3 legend for notations.

administration. However, during 20 min of observation the ethanol-saline vehicle did not change the low voltage, fast wave EEG pattern characteristic of the untreated animal (Fig. 4).

Three cats (C, D, E) with chronically implanted EEG electrodes were injected with different concentrations of PGD_2. The EEG record of one of these cats (C), obtained during an 8-hour period in the absence of drug administration, typically showed a low voltage, fast wave activity interrupted occassionally by slower waves of 1–2 sec duration (Fig. 5). When cat C was administered 30 μg PGD_2 no change in the EEG pattern was noticed until 10 min after exposure to the drug when spindle-type high voltage, slow waves appeared on the EEG record. These slow waves were more prominent 50 min post-drug (Fig.5) and returned to the low voltage, fast wave form when the animal was alerted by noise, but reappeared immediately following the alert. High voltage, slow-waves continued to appear on the EEG recording 65 min post-PGD_2. When cat C was administered higher doses of PGD_2 (100, 300, and 900 μg), high voltage, slow waves appeared on the EEG record as early as 2 min after administration of the drug, and the slow wave pattern dominated the record for at least 60 min post-PGD_2 infusion (Fig. 5). When the animal was alerted by loud noise during periods of slow wave recording, the EEG responded with low voltage, fast waves which reverted back to the higher voltage slow wave form upon termination of the stimulus. This active cat had pronounced behavioral responses to 300 and 900 μg PGD_2; he showed symptoms of diarrhea and abdominal contractions, relaxed nictitating membranes, and he maintained a stationary crouching posture with head bowed for long intervals. Only after administration of 900 μg PGD_2 did cat C show signs of ataxia and analgesia (as evidenced by failure to withdraw the right paw after pinching of the footpad) within 15 min after PGD_2 infusion.

Another cat (D) when administered 100 μg PGD_2 responded immediately with an opisthotonos convulsion (head extended backward and front limbs extended in a tetanic spasm), vocalization, and failure to respire. After several minutes of artificial respiration, the cat began to breathe spontaneously but did not regain consciousness until 37 min post-PGD_2 when he exhibited catatonia (failure to return raised and extended forelimb to normal position), ataxia, abdominal contractions, relaxed nictitating membranes, and analgesia (see above). The EEG record showed characteristic high voltage activity during the convulsion, and after recovering consciousness the cat's EEG showed post ictal depression and frequent high voltage, slow waves. The latter were not reversed by auditory or tactile stimuli. One week later, cat D was treated with 50 μg PGD_2. The lower dose of PGD_2 did not result in convulsion; however, the animal appeared sedated 30 min post-PGD_2 when intermittent high voltage, slow waves appeared on the EEG recording and the animal showed little spontaneous movement. After 60 min, the cat sat in one position continuously with eyes closed, and there was almost continuous high voltage, slow wave EEG activity. The slow waves were partially reversed to low voltage, fast waves after 70 min, and an active low voltage, fast wave pattern dominated the EEG recording for 2–4 hours post-PGD_2 during which time the cat's eyes were open, and

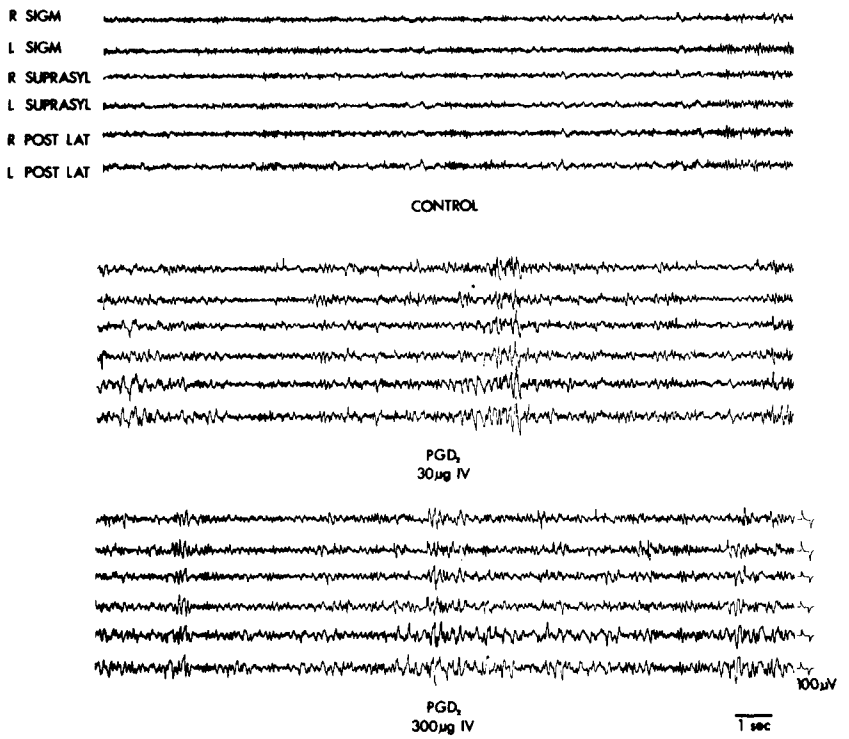

FIG. 5. Sedative effects of PGD_2 in a chronically prepared, unrestrained cat (C). Time of recording after drug administration: PGD_2 (30 μg), 50 min; PGD_2 (300 μg), 60 min. See Fig. 3 legend for notations.

the animal was alert. A week later a second administration of 100 μg PGD_2 to cat D resulted in an opisthotonos convulsion, respiratory failure and death.

A third cat (E) with chronic EEG electrode implants was administered 100 and 1000 μg PGD_2 on different days. The lower dose of PGD_2 (100 μg) lowered the voltage of the EEG recording and within 10 min post-drug the animal appeared sedated, sitting in a crouch position for long periods with head lowered, and eyes almost closed with a slight relaxation of the nictitating membranes. The higher dose of PGD_2 (1000 μg) caused the animal to salivate, and attempt to vomit and defecate immediately. The nictitating membranes were partly relaxed, and respiration was rapid (86–102 breaths per min, compared to a normal rate of 25–30 breaths per min) during 30 min of observation. Noise did not elicit reflex movement of any kind, and 20 min post-drug the animal exhibited an analgesic response (see above). Within 30 min post-PGD_2, the animal appeared more alert and responded to noise with both ear and eye reflex movement, and 35 min post-drug the cat retracted its foot after a toe pinch. The EEG recording of cat E reflected the sedated behavioral responses since high voltage, slow wave activity of the type recorded for cat C (Fig. 5) was noted 20 min post-PGD_2.

DISCUSSION

The results of these studies demonstrate that PGD_2 produced a sedative effect in rodents and cats. The sedative properties of PGs of the E-type have been well documented for rats [6,17], mice [22], cats [10,11], and monkeys [5,17]. On the other hand, $PGF_{2\alpha}$ has been described as lacking in sedative properties in the cat [10], adult fowl [15] and the rat [16], and PGA_1 had no effect on locomotor activity in the rat [16]. In our studies, 0.4–4 mg/kg PGD_2 significantly reduced SLMA in rats, and sedated cats, whereas similar concentrations of PGE_1 impaired SLMA of chicks [11] and mice [22]. In addition, the intravenous administration of PGD_2 (0.4, 2.5, and 8 mg/hr) to a Rhesus monkey decreased spontaneous activity and increased the frequency and length of sleep episodes in the animal in a dose-related manner (S. Laychock, unpublished observations). Thus, PGD_2 appears to possess sedative activity similar to equivalent doses of PGE_1. Pharmacological concentrations of PGD_2 were used, since studies have shown that the peripheral administration of PG results in a large percentage (80–90%) of PG being metabolized before reaching the brain [8] where it is found in small quantities [7].

Similarities between PGD_2 and other PGs are also noted when comparing effects on barbiturate anaesthesia. Studies have shown that PGE_2 potentiates the analgetic and anaesthetic effects of pentobarbital in rats [6], and PGE_1 and $PGF_{2\alpha}$ potentiate the duration of hexobarbitone-induced sleep in mice [18]. In our studies, similar doses of PGD_2 also potentiated barbiturate sleeping time of mice; however, the only analgetic response to PGD_2 noted in our studies was during the administration of this PG to cats.

While PGD_2 and the PGEs appear similar in several of their pharmacological effects, some of our results using PGD_2 contrast with the effects of other PGs on parameters such as neuromuscular coordination and anticonvulsant activity. Unlike the neuromuscular incoordination of PGE_1-treated mice [22], PGD_2-treated mice maintain coordination when challenged by the rotarod performance test; similarly,

only at high doses of PGD_2 was ataxia noted in cats. The lack of a protective effect of PGD_2 on the convulsive activity of pentylenetetrazol or electroshock in our studies are in contrast to the previously reported effect of PGE_1 in retarding the onset of pentylenetetrazol convulsions in rats [3] and inhibiting the electroshock convulsions [14]. Indeed, PGD_2 precipitated tetanic convulsions in one cat. But, also in contrast to PGE_1, $PGF_{2\alpha}$ facilitates pentylenetetrazol-induced convulsions [14]. Thus, no common effect of PGs on convulsant activity is apparent.

The sedative effects of PGD_2 were reflected in changes induced in the EEG recordings of cats administered PG. However, correlation between behavioral changes observed in rats and cats, and EEG changes in cats in response to PG must remain inferential. The cats in our studies demonstrated EEG wave forms characteristic of waking (low voltage, fast waves) and sleeping (high voltage, slow waves) [4]. PGD_2 administration evoked varying degrees of slow wave activity, with the highest voltage, slow waves accompanying the injection of high concentrations of PGD_2. However, due to the variability in animal responses, no strict dose-dependent effect of PGD_2 on amplitude or duration of slow wave activity was demonstrated. The slow wave activity usually reverted transiently to the fast wave form when the animal was aroused, suggesting that the sedative effect of PGD_2 could be temporarily modified by external stimuli. Similar effects of other PGs on cortical activity have been reported. In the monkey, PGE_1 decreased the rate of spontaneous discharge of impulses in neurons in the cortex and desynchronized the EEG [5], while PGE_2 also decreased the power of the EEG [17]. In fowl, PGE_2 evoked electrocortical sleep characterized by large amplitude, slow frequency waves [15]. $PGF_{2\alpha}$ lacked effect on the EEG of the monkey [5] or fowl [15]. In the rat, on the other hand, PGE-induced sedation was accompanied by paradoxical sleep patterns [8].

Whether or not the effects of PGD_2 on EEG activity in cats, and sedative behavior in the other species studied, were due to a direct effect of PGD_2 on the central nervous system or due to effects of PG on cerebral blood flow or other physiological parameters is an open question. The effects of PGs on vascular contractility and blood pressure have been well documented [9]. PGD_2 has been described as a pressor agent in sheep and rabbits [12], whereas in our studies this PG decreased the mean blood pressure in the cat. PGD_2 also decreased the mean blood pressure in a monkey (S. Laychock, unpublished observation). In addition to blood pressure, PGs also affect heart rate [10] and PGD_2 caused a slight bradycardia in cats.

The authors recognize that ethanol in the drug vehicle may be in part responsible for the changes seen in blood pressure or behavior after PG administration. However, whereas ethanol alone caused a fall in blood pressure in the cat, the pressure rapidly returned to normal and there was no change in the EEG pattern. Thus, changes in blood pressure alone were not sufficient to alter the voltage and frequency of the EEG as described. PGD_2 in ethanol vehicle, on the other hand, produced a prolonged decrease in the cat's blood pressure and evoked changes in cortical activity which were not seen with ethanol alone. Other researchers report that, unlike PGs, ethanol increased the discharge frequency of cortical neurons in the monkey [5] and produced none of the behavioral or physiological changes induced by PGs in the rat [8]. Thus, it is likely that PGD_2 does have direct effects on the central nervous system.

These studies demonstrate that PGD_2 shares many of the behavioral and pharmacologic properties of other PGs. We have described the major effects of PGD_2 on locomotor activity, barbiturate sleeping time, blood pressure, and EEG activity, and these findings taken together with evidence demonstrating relatively high concentrations of PGD_2 in the brain of several species [1,2], support the concept that PGD_2 may serve a physiological role in the central nervous system. On the other hand, brain PGs may also serve to modulate the activity of peripheral physiological (hormonal) systems through actions on the hypothalamus or adenohypophysis [19].

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