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Inhibition of Penicillin-Induced EEG Discharges by Low Doses of Morphine or Naloxone in the Rabbit. Evidence for a Possible Non-Opioid Receptor-Mediated Mechanism at the Sensorimotor Cortex

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SPILLANTINI, M. G. AND M. MASSOTTI. *Inhibition of penicillin-induced EEG discharges by low doses of morphine or naloxone in the rabbit. Evidence for a possible non-opioid receptor-mediated mechanism at the sensorimotor cortex.* PHARMACOL BIOCHEM BEHAV **24**(5) 1241–1246, 1986.—In rabbits, pretreatment by intravenous (IV) and intracortical (IC) routes with low doses of morphine (250 μg/kg IV or 60 pmoles/rabbit IC) and naloxone (1–50 μg/kg IV or 0.3 pmoles/rabbit IC) antagonizes the EEG and behavioural seizures due to the IC injection of penicillin (150 Units) at the level of the sensorimotor cortex. Pretreatment with naloxone (20 μg/kg IV) did not alter the anticonvulsant effect of morphine (250 μg/kg IV). The similar anticonvulsant effect of the two drugs together with the absence of any antagonism by naloxone on the effect of morphine seem to suggest that both drugs act through a non-opioid receptor-mediated mechanism. Further, in light of the low effective doses of the drugs and of the absence of any additive effect after their combined administration, one might speculate that morphine and naloxone do not act through different pharmacological receptors. However, the presence of distinct EEG patterns with either morphine or naloxone, injected IC and IV, in animals fully protected against penicillin-induced seizures, does not seem to be in favour of the latter possibility.

Rabbit convulsions EEG Naloxone Morphine Penicillin

THE role of the brain's opioid systems in regulating convulsive phenomena is intriguing. Both convulsant and anticonvulsant effects have been described following the administration of either opiate agonists or antagonists. Earlier observations of the proconvulsant and convulsant effects of large doses of either morphine [2, 20, 28] or naloxone [8, 18, 21, 24] have been later attributed to mechanisms not mediated through opioid receptors [8, 10, 12, 18, 21, 30]. On the other hand, anticonvulsant effects of opiate agonists have been also observed with much lower doses. For instance, morphine displays anticonvulsant effects at doses which are in the range of the analgesic and cataleptic doses [1, 5, 6, 14, 21, 26, 27]. More recently, data from our laboratory showed that morphine at doses lower than those producing analgesia blocks the convulsions due to drugs which reduce γ-aminobutyric acid (GABA) synaptic activity [17, 18, 21], and that this effect was not antagonized by naloxone [18,21]. On the other hand, data from the literature have clearly shown that naloxone is able to block the opiate-induced seizures [10,23]. One report, however, demonstrated that naloxone (2 mg/kg IP) inhibits the convulsions due to non-opiate drugs, i.e., in response to the withdrawal of ethanol in mice [3].

The present study was designed to explore whether or not very low doses of naloxone possess inhibitory effects toward non-opioid-induced discharges, such as those elicited by intracortical injection of penicillin to rabbits. Penicillin produces seizures by reducing GABA mediated transmission [7] through a weak picrotoxin-like effect, i.e., impairment of chloride conductance [13].

METHOD

Acute experiments were performed on a total of 99 male

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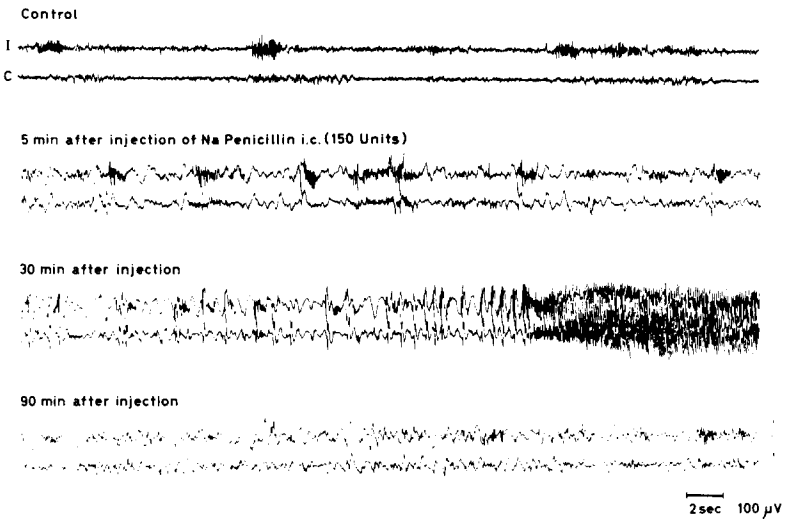

FIG. 1. EEG effects of IC injection of Na penicillin in rabbits. Typical EEG pattern observed at the various times after injection of 150 Units of penicillin into the sensorimotor cortex. For the number of animals see Table 1A. Note the presence of the spikes mainly in the ISM 5 min after penicillin. Leads: 1, sensorimotor cortex ipsilateral to the hemisphere of injection of penicillin (ISM). C, sensorimotor cortex contralateral to the hemisphere of injection of penicillin (CSM).

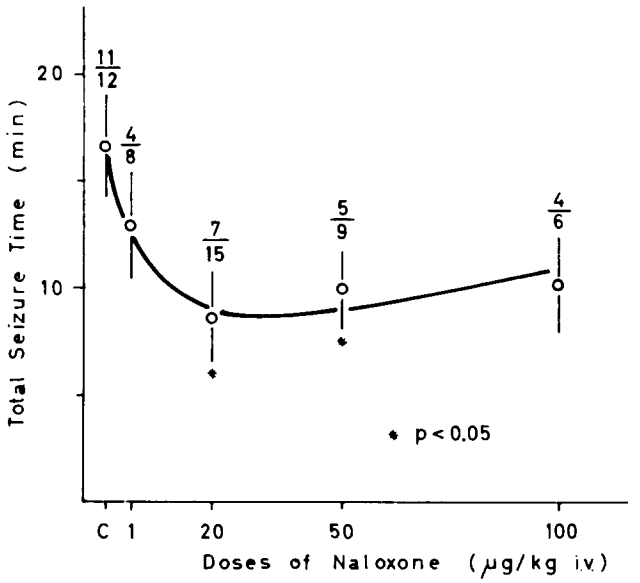

FIG. 2. Effects of naloxone IV on the seizures due to penicillin in rabbits. The various doses of naloxone (abscissa) were administered IV 5 min before IC injection of penicillin (150 Units). The ratios represent the number of animals showing seizures over the number of animals tested. The values of TST (ordinate) were calculated only in the animals showing convulsions. A decrease of the incidence of seizures occurs at the doses of 1–50 μg/kg, whereas the values of TST decrease at the doses of 20 and 50 μg/kg. *$p<0.05$, statistically different from the group pretreated with saline IV (C), according to the Student's t-test.

TABLE 1

OCCURRENCE OF "GRAND-MAL" EEG SEIZURES AFTER INJECTION OF PENICILLIN (150 UNITS) IC TO RABBITS. EFFECT OF THE INJECTION OF MORPHINE OR NALOXONE BY IV OR IC ROUTES

		No. of animals showing convulsions / No. animals injected	TST per convulsant animal (min±SEM)
A Saline	1 ml/kg IV	11/12	16.6 ± 4.8
Naloxone	20 μg/kg IV (61 nmoles)	7/15	8.7 ± 3.1*
Morphine	250 μg/kg IV (876 nmoles)	4/9	6.4 ± 1.8*
B Saline	20 μl IC	7/8	13.8 ± 2.8
Naloxone	0.3 pmoles IC	1/5	1.6
Morphine	60 pmoles IC	3/7	2.5 ± 1.8*

TST values are calculated only in animals showing convulsions.
*$p<0.01$ statistically different in respect to the values found with saline according to the Student's t-test.

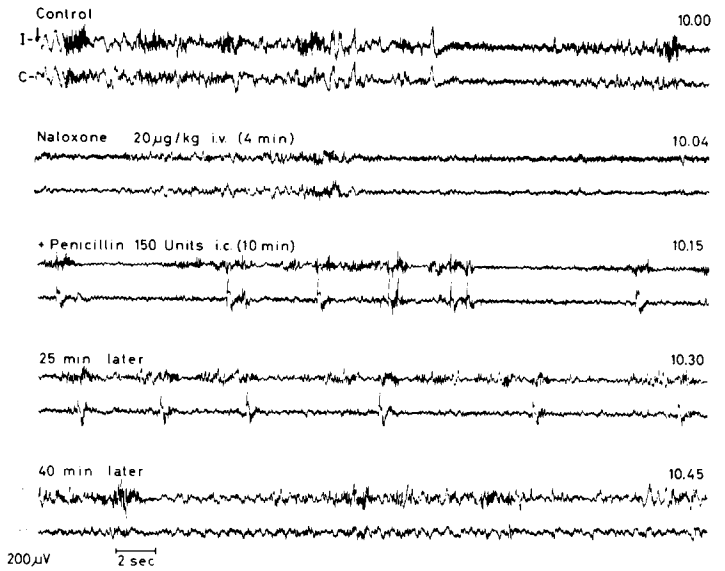

FIG. 3. Effects of pretreatment with naloxone IV on the EEG changes due to IC injection of penicillin in rabbits. Typical EEG pattern observed in animals fully protected by a dose of 20 μg/kg IV of naloxone from the EEG and behavioural seizures due to IC injection of penicillin (150 Units). For the number of the animals, see Table 1A. The decrease of the voltage observed after naloxone was observed in 5 of the 10 animals protected towards the seizures. Note the presence of spikes more pronounced at CSM. Leads: as reported in Fig. 1.

rabbits weighing 2.0–2.5 kg. Four screw electrodes were implanted on the skull under local anaesthesia (2% xylocaine), at the level of the anterior and posterior sensorimotor cortices of both hemispheres. In addition, a hole was drilled 4 mm from the longitudinal suture on the coronary suture, to allow the injection of penicillin.

The convulsive activity was produced by Na penicillin (150 Units/rabbit) injected intracortically (IC) in a volume of 20 μl, at a depth of 1 mm from the surface.

Morphine-HCl and naloxone-HCl were dissolved in saline. The drugs were injected 5 min before penicillin through either intravenous (IV) or IC routes. The IC injection of the opiates was carried out in the same site as injection of the penicillin in a volume of 20 μl. Control animals were injected with saline 20 μl/rabbit IC or 1 ml/kg IV. Doses are referred as free base.

The effects of the combined administration of naloxone and morphine was also assessed. The experiment consisted of five replications each using four animals, challenged with the following treatments: (A) saline 1 ml/kg IV, 5 min later saline 1 ml/kg IV, 5 min later penicillin 150 Units IC; (B) naloxone 20 μg/kg IV, 5 min later saline 1 ml/kg IV and 5 min later penicillin IC; (C) saline 1 ml/kg IV, 5 min later morphine 250 μg/kg IV and 5 min later penicillin IC; (D) naloxone 20 μg/kg IV, 5 min later morphine 250 μg/kg IV and 5 min later penicillin IC.

The electroencephalogram (EEG) was recorded continuously beginning 30 min before the drug administration and continuing until it returned to the pre-drug pattern (about one hour and a half in control animals). Two leads were recorded: the first showed the electrical activity at the sensorimotor cortex of the hemisphere ipsilateral to the side of injection of penicillin, hereafter referred to as ISM; the second showed the electrical activity of the contralateral hemisphere, hereafter referred to as CSM. In animals showing convulsions, the duration of all seizures was summed and defined as total seizure time (TST).

Although the animals were partially restrained, several signs indicating sedation or excitation could be noticed.

RESULTS

Effects of the IC Injection of Penicillin

Intracortical injection of penicillin (150 Units) produced within a few min the characteristic progression from EEG isolated spikes in the ISM to repeated ictal events (Fig. 1). Each seizure lasted 20 to 90 sec and was followed by an interictal period characterized by either an almost isoelectrical pattern or high voltage waves, both accompanied by high voltage spikes, lasting 1 to 5 min.

A mean of 16 seizure attacks per animal was observed in 11 of the 12 penicillin-treated animals (Table 1A), beginning 9 min after the injection of the drug. The effect of penicillin lasted approximately 60 min and the value of TST was 16 min. The recovery period, lasting approximately 30 min, was characterized by high voltage waves intermingled with spikes. Pretreatment with saline IC did not significantly affect the convulsant effect of penicillin, as evidenced by measurement of TST value (Table 1B).

From the behavioural point of view, the isolated spikes were associated with muzzle myoclonus and jerks of the limbs. Signs of excitation were also noticed, consisting of head-up, struggling and startle reaction to the rattling noise. The EEG seizures were preceded by slow rotation of the head and nystagmus, and were associated with tonico-clonic convulsions.

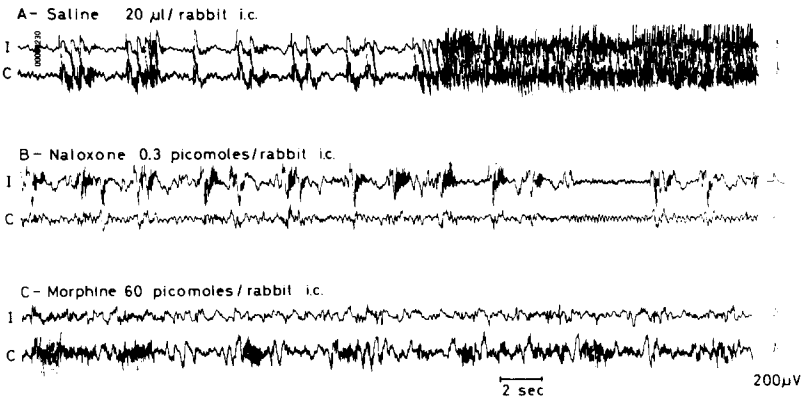

FIG. 4. Effects of pretreatment with naloxone and morphine IC on the EEG changes induced by penicillin IC in rabbits. Typical EEG patterns observed 15 min after IC injection of penicillin (150 Units) in rabbits pretreated IC, 5 min before, with: A, saline (20 µl/animal); B, naloxone (0.3 pmoles/animal); C, morphine (60 pmoles/animal). Note at ISM the presence of spikes in animals pretreated with naloxone (B) and the slowing in animals pretreated with morphine (C). For the number of animals, see Table 1B. Leads: as reported in Fig. 1.

Effects of the Low Doses of Naloxone on the Convulsions due to Penicillin

Naloxone was injected at doses of 1–100 µg/kg (3–305 nmoles/kg) IV or 0.30 pmoles/rabbit IC, 5 min before penicillin (150 Units). The IV injection of naloxone (1–100 µg/kg) does not induce consistent EEG changes. Conversely, signs of slight behavioural sedation (head drop, absence of struggling and weak or no reaction to a rattling noise) were noticed within one min after injection.

Pretreatment with 1–50 µg/kg IV of the opiate antagonist significantly reduced (40–50%) the occurrence of EEG and behavioural seizures due to the subsequent injection of penicillin. In the group of animals showing convulsions, however, a decrease of the values of TST was noticed, which achieves statistical significance only in animals pretreated with 20 and 50 µg/kg IV of naloxone (Fig. 2 and Table 1A). A reduction of the number of motor convulsions was also noticed. In the group of animals fully protected by naloxone (20 µg/kg IV), within 10 min after injection of penicillin, the EEG pattern showed isolated spikes, which were more pronounced in the CSM. During the following 5 min, however, a reduction in both the incidence and amplitude of the spikes was noticed only in the ISM (Fig. 3). Recovery occurred 40–60 min after penicillin. The spikes were not always associated with muzzle myoclonus and jerks of the forelimb ipsilateral to the side of injection of penicillin. Signs of sedation were also observed.

The IC administration of naloxone (0.3–1.0 pmoles/rabbit) also induce signs of behavioural sedation not associated with consistent changes of the EEG pattern. The opiate antagonist protects the animals from the EEG and behavioural convulsions induced by the subsequent injection of penicillin. As shown in Table 1B, only 1 of the 5 rabbits pretreated with naloxone (0.3 pmoles/rabbit IC) showed a short-lasting period of EEG and behavioural seizures after penicillin. In the other animals, within a few min after injection of penicillin, spikes and spike-and-wave complexes, spindles and slow waves were noticed. They were mainly present in the ISM (Fig. 4B). Behaviourally, the spikes were not always associated with jerks of the contralateral forelimbs. The signs of sedation were also present.

Effects of the Low Doses of Morphine on the Convulsions due to Penicillin

Morphine was injected at the doses of 250 µg/kg (876 nmoles/kg) IV or 60 pmoles/rabbit IC, 5 min before penicillin (150 Units).

As previously reported [17], pretreatment with a dose of 250 µg/kg IV of morphine substantially decreased the incidence of the seizures due to penicillin. In animals showing convulsions, the values of TST (Table 1A) and the number of the EEG ictal events were also reduced. In animals fully protected from the seizures, scattered spikes occurred, more pronounced in the ISM.

The IC injection of morphine (60 pmoles/rabbit) also protected 50% of the animals from the EEG and behavioural seizures due to the subsequent injection of penicillin. In the animals showing convulsions, however, significant reductions in the number of both the ictal events and of the values of TST (Table 1B) were noticed.

The IC injection of morphine did not induce consistent changes of EEG. In animals fully protected by morphine, after injection of penicillin a reduction of voltage and slow waves were observed in the ISM, whereas, slow waves spindles and spikes were noticed in the CSM (Fig. 4C).

Behaviourally, signs of sedation were observed after both IV and IC injection of morphine. These were also present in animals fully protected against the seizures, and were accompanied by muzzle myoclonus and jerks of the ipsilateral forelimb.

Effects of Combined IV Administration of Naloxone Plus Morphine on the Convulsions due to Penicillin

In animals injected with the combination of morphine and naloxone, no significant difference in the penicillin-induced convulsions was noticed compared to the single pretreatments (Table 2, compare treatment D versus treatments B and C). In four of the five replications, the combined treat-

TABLE 2

EEG AND BEHAVIOURAL EFFECTS OF IC PENICILLIN (150 UNITS) IN RABBITS WITHOUT OR WITH PRETREATMENT BY NALOXONE, MORPHINE OR BOTH

Pre-treatments		REPLICATIONS 1	2	3	4	5
A) Saline	EEG	Seizures (TST=9 min)	Seizures (TST=13 min)	Seizures (TST=17 min)	Seizures (TST=11 min)	Seizures (TST=16 min)
	Behav.	Convulsions	Convulsions	Convulsions	Convulsions	Convulsions
B) Naloxone 20 μg/kg IV	EEG	spikes (CSM>ISM)	Seizures (TST=1.5 min)	spikes (CSM>ISM)	spikes (CSM>ISM)	spikes (CSM>ISM)
	Behav.	Sedation	Convulsions	Sedation Myoclonus (i)	Sedation Myoclonus	Sedation
C) Morphine 250 μg/kg IV	EEG	spikes (ISM>CSM)	Seizures (TST=2 min)	spikes (ISM>CSM)	Seizures (TST=5 min)	spikes (ISM>CSM)
	Behav.	Sedation Myoclonus (c>i)	Convulsions	Sedation Myoclonus (c)	Convulsions	Sedation
D) Naloxone + Morphine	EEG	spikes (ISM)	Seizures (TST=2 min)	spikes (ISM>CSM)	spikes (ISM=CSM)	no spikes
	Behav.	Sedation	Convulsions	Sedation	Sedation	Sedation

The experiment consisted of five identical replications each using one animal in each of the pretreatment conditions.
ISM and CSM, see legend in Fig. 1.
i=forelimb ipsilateral to the hemisphere of injection.
c=forelimb contralateral to the hemisphere of injection.

ment fully protected the animals from the penicillin-induced seizures. The EEG patterns showed, in two animals, the prevalence of spikes at ISM (replications No. 1 and 3), whereas another showed spikes both at ISM and CSM (replication No. 4), and the last rabbit did not exhibit spikes (replication No. 5). Behaviourally, the animals showed signs of sedation; in no case was myoclonus noticed.

Similar effects were also observed with the doses of 1 and 50 μg/kg IV of naloxone (data not shown).

DISCUSSION

Based on EEG studies in the rabbit, the present study shows that extremely low doses of either morphine or naloxone inhibit the penicillin-induced discharges. In both cases the effects are competitive, since morphine [17] and naloxone (data not shown) both counteract the effects of low doses (75 and 150 Units), but not of high doses (300 and 600 Units), of penicillin. Penicillin induces convulsions by reducing GABA-mediated transmission [7], hence it is likely that the effects of morphine and naloxone could be ascribed to an enhancement of GABA synaptic activity. An anticonvulsant effect of the low doses of morphine mediated by a facilitation of GABA synaptic activity has been already hypothesized [17, 18, 21].

The similarities of effects of morphine and naloxone described here are analogous to the findings that both drugs enhance memory [19], inhibit feeding, drinking in normal rats [11] and mating in castrated rats [15]. Decrease of EEG alpha frequency and hypothermia have been also reported in humans after either naloxone [29] or morphine [31]. Since it has been reported that the sedative-anticonvulsant ([17]; present data) and the anorectic [11] properties of morphine are not antagonized by naloxone, one can suggest that under these experimental conditions, morphine acts through a non-opioid receptor-mediated mechanism. Marçais [16] and Urca and Frenk [27] hypothesized that two opiate systems exist in the central nervous system. One is excitatory and epileptogenic, sensitive to the high doses of opiate agonists and to the antagonism by naloxone. Another is sensitive to the low doses of the opiates, possesses inhibitory and antiepileptic properties and is insensitive to the antagonism by naloxone. The latter, according to our data, seems to display agonist-like effects.

The observation that an anticonvulsant effect of both drugs is also found after IC injection suggests that in the rabbit the sensorimotor cortex possesses a tonically active mechanism in gating the anticonvulsant effect of the low doses of morphine and naloxone, which may not be opioid in nature. This hypothesis is strengthened by the observation that morphine iontophoretically applied in the rat cortex can elicit both opioid and non-opioid effects [22]. A similar finding has been also found in the rat brain stem [4].

Morphine and naloxone inhibit the penicillin-induced discharges at very low doses. The finding that their anticonvulsant effects are not additive, as observed in the case of the combined administration of morphine plus naloxone, seems to support the possibility (but does not prove) that the two drugs do not act through different receptors. Frenk and Rogers [11] suggested a similar conclusion to explain the ability of both the opiate agonist and antagonist in inhibiting feeding and drinking in the rat.

The possibility that a common mechanism mediates the anticonvulsant effects of morphine and naloxone does not seem, however, to be confirmed by the finding that distinct EEG features are observed after IV or IC injection of either

morphine or naloxone. Only after morphine IV and naloxone IC do common EEG patterns occur, which indicate an inhibition of the spreading of the ictal event. The effect of morphine is consistent with the reported ability of the drug to antagonize the maximal electroshock seizures (MES) [9]. According to Swinyard and Castellion [25], a reduction of MES is mainly related to an inhibition of the spreading of the seizures.

The EEG patterns observed after morphine IC and naloxone IV are rather difficult to explain. One could speculate that morphine IC reduces the voltage and the frequency because of a local effect of the drug (for instance related to changes of the ionic compartmentation). As far as the effect of naloxone IV is concerned, no explanation is available at present. However, while following the antagonist, spikes occur mainly at CMS (present data), after morphine IV, they occur at ISM ([17]; present data), and after the mixed agonist-antagonist cyclazocine IV, they occur both at ISM and CSM [17].

In conclusion, the present data indicate that a non-opioid receptor-mediated mechanism is present at the level of the sensorimotor cortex of the rabbit, which mediates the anticonvulsant effect of the low doses of morphine and naloxone. Further studies are required to clarify the molecular mechanism by which morphine and naloxone elicit such a common effect.

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