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Pro- and Anticonvulsant Action of Morphine in Rats

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URCA, G. AND H. FRENK. *Pro- and anticonvulsant action of morphine in rats.* PHARMAC. BIOCHEM. BEHAV. 13(3) 343–347, 1980.—Rats were pretreated either with saline or with various doses of morphine. Thirty minutes following this pretreatment animals received an injection of either naltrexone (5 mg/kg) or saline. Motility was measured following the second injection. All animals then received 40 mg/kg pentamethylenetetrazol (PTZ). Morphine, but not naltrexone, showed anticonvulsant action by increasing the latencies to the first preclonic jerk and seizure onset. In addition, morphine tended to shorten seizure duration, whereas naltrexone tended to lengthen it. However, at the most effective anticonvulsant dose morphine-treated animals showed significantly more convulsive seizures than did the saline-treated controls. The continuation of these multiple seizures was blocked by naltrexone. At doses which did not lower preseizure motility but rather increased it, morphine significantly enhanced the duration of the behavioral post-ictal depression (PID). Naltrexone, though effecting preseizure motility when administered after morphine, did not effect PID. These results are taken as evidence, that morphine possesses both pro- and anticonvulsant properties, depending on the prior occurrence of a PTZ-induced seizure. The possibility that seizures cause increased sensitivity of the organism to morphine is discussed.

Morphine Pentamethylenetetrazol Convulsions Anti-epileptic opiates

THE convulsant potential of opiates as reflected both by EEG and behavior has been demonstrated in various species [4, 8, 18]. More recently it has been shown that endogenous opioids (methionine—and leucine-enkephalin, β-endorphin) share this epileptogenic potential [8, 11, 16, 17].

Naloxone, which blocks the convulsant actions induced both by opiate agonists [8,9] and endogenous opioids [8,11], has also been reported to produce convulsions when administered by itself in the pigeon and squirrel monkey [10] and in mice [9].

Moreover, both morphine and naloxone have been found to have synergistic interactions with behavioral and electrographic seizures induced by other agents. Morphine has been shown to potentiate convulsant phenomena when administered with picrotoxin in rabbits [12], strychnine in frogs [15] and pentamethylenetetrazol (PTZ) in mice [14]. Naloxone has been reported to potentiate the convulsant action of bicuculline, but not strychnine in mice [5] and has also been shown to increase seizure incidence in the genetically seizure prone gerbil [2], although no changes have been seen by others in the same species [7].

On the basis of the evidence summarized above, it could be concluded that opiate agonists and antagonists are essentially proconvulsants. However, anticonvulsant effects of these agents have also been demonstrated. Adler *et al.* [1] have shown that administration of morphine at high doses (e.g. 64 mg/kg) raised the threshold to PTZ and flurothyl-induced convulsions in rats and also significantly increased the latency to the first preclonic jerk and full seizure induced by PTZ. In addition, naloxone has been reported to reduce alcohol withdrawal seizures in mice, suggesting an anticonvulsant action for this substance in certain cases [3].

The present experiment sought to study further the pro- and anticonvulsant properties of opiate agonists and antagonists and to determine whether the discrepant reports could be reconciled.

METHOD

Male albino rats weighing 400–450 g of the "sabrah" strain were maintained on a reversed light cycle (light on between 8.00 p.m. and 8.00 a.m.) with water and food pellets ad lib. Testing took place between 10.00 a.m. and 4.00 p.m.

The drugs used in this experiment were morphine hydrochloride (administered at 5, 15, or 50 mg/kg), naltrexone hydrochloride (5 mg/kg), pentamethylenetetrazol (PTZ, 40 mg/kg), and physiological saline. All drugs were dissolved in physiological saline and all injections, except for morphine 50 mg/kg, were administered intraperitoneally in a volume of 1 ml/kg. Morphine 50 mg/kg was administered as 2 ml/kg.

Four groups of animals were pretreated with saline, 5, 15 or 50 mg/kg of morphine. Thirty minutes following the first injection part of the animals in each group received 5 mg/kg of naltrexone (SaNa or MoNa-naltrexone groups), and the remaining animals received 1 ml/kg of saline (SaSa or MoSa-morphine groups). Motility was measured immediately following the second injection. Animals were placed in a box measuring 40×25 cm, the floor of which was divided into 4 equal rectangles. The number of squares crossed during each minute of this test period was counted and used as a measure of the motility of the animals. Testing lasted for 5 min. At the end of this period animals were injected with PTZ (40 mg/kg) and placed in the motility box. Latencies to the first preclonic jerk (PCJ), seizure onset, and duration of the first seizure were recorded. Following the

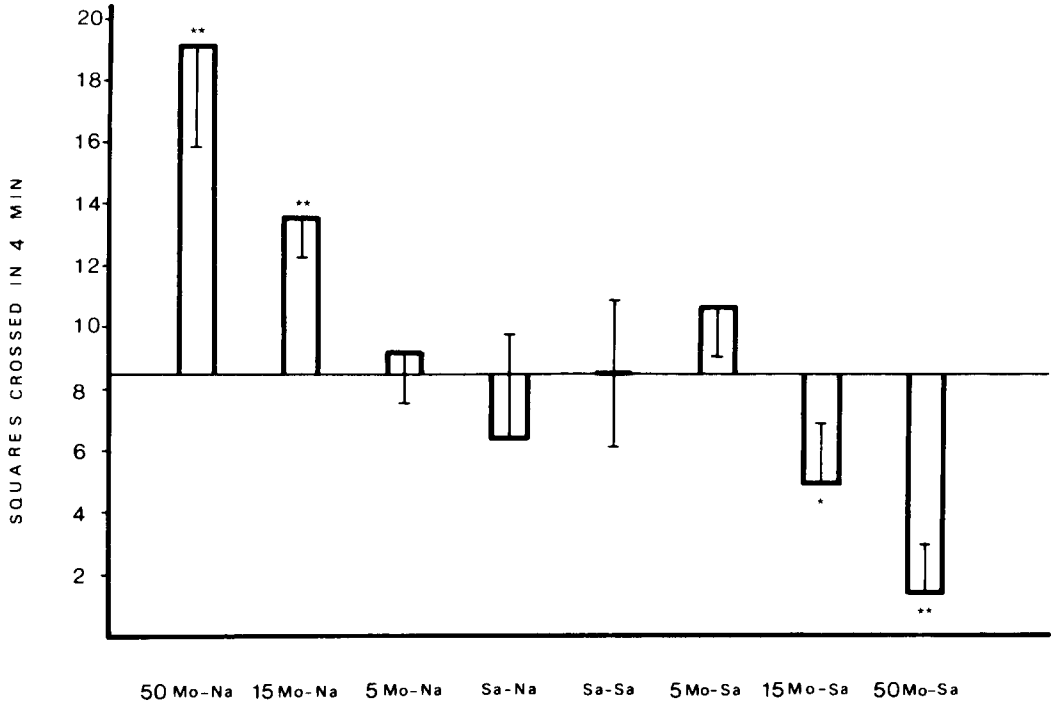

FIG. 1. The effects of morphine and naltrexone pretreatment on motility $^{*}p<0.05$ when compared to SaSa.

first seizure behavioral post-ictal depression (PID) duration was monitored. PID was defined as the time interval between termination of the first seizure and the first spontaneous step forward. Animals were observed for 15 min after the onset of PID and the incidence of repeated tonic-clonic convulsions, if such occurred, was noted. Animals belonging to group 50 MoSa that showed repeated convulsions were then injected with either saline or naltrexone (5 ml/kg). The incidence of convulsions was monitored for 30 more minutes, unless death occurred before this time period elapsed.

RESULTS

Statistical evaluation of the data was performed using analysis of variance or, in cases of paired comparisons, the student t-test.

Preseizure Motility

In order to assess the level of activity, motility scores during the last 4 min of the 5 min post-injection observation period were analyzed. The reason that only part of the observation period was analyzed was that in the MoNa groups naltrexone-induced activation could be seen only after the drug had taken effect, approximately 1 min following the injection, thus rendering the first minute irrelevant for the purpose of the experiment. Motility scores obtained when all 5 min of the observation period were included showed a qualitatively similar profile although not of the same magnitude.

A significant difference in motility was observed between morphine (MoSa, SaSa), and naltrexone (MoNa, SaNa) pretreated animals, $F(1,58)=20.84$, $p<0.01$. As can be seen from Fig. 1, administration of morphine resulted in a marked inhibition of motor activity, whereas increased activity was observed when morphine injections were followed by naltrexone. A clear dose related decrease of motility was observed in the MoSa groups, with the highest dose of morphine inducing the strongest behavioral depression. In contrast, the greatest behavioral excitation occurred when naltrexone followed the highest dose of morphine.

PTZ-Induced Convulsions

Table 1 summarizes the incidence of PTZ-induced seizures in the various groups. Except for the higher incidence of multiple seizures in group 50-MoSa no significant variations between the groups were observed.

Latencies to the First Preclonic Jerk (PCJ) and Seizure Onset

Only animals displaying seizures were included in this analysis. Comparison of morphine and naltrexone pretreated animals reveals a significant treatment effect for both latency to PCJ, $F(1,46)=8.64$, $p<0.01$, and seizure onset, $F(1,46)=10.25$, $p<0.01$. A significant Treatment×Dose interaction, $F(3,46)=5.84$, $p<0.01$, indicates that morphine, but not naltrexone, was effective in changing the latency to PCJ and seizure onset (Fig. 2). Morphine increased the latencies to both events in a dose related fashion, with the highest dose of morphine increasing significantly the latencies to PCJ and seizure onset by 104 and 165%, respectively, when compared to saline pretreated animals ($p<0.005$ for both comparisons). Animals receiving 15 mg/kg of morphine also showed significantly longer latency to the first seizure ($p<0.05$). None of the groups receiving naltrexone differed significantly from the control animals.

Duration of the First PTZ Seizure

Significant differences between morphine followed by saline (MoSa, SaSa) and morphine followed by naltrexone (MoNa, SaNa) could be seen when the duration of the first

TABLE 1

INCIDENCE OF PTZ-INDUCED SEIZURES IN THE GROUPS OF TREATMENT

Group	One seizure	No seizures	Multiple seizures	Status* epilepticus	Total animals (n)
50 MoNa†	3	0	1	1	5
15 MoNa	5	1	0	2	8
5 MoNa	5	0	0	0	5
SaNa	3	0	2	0	5
SaSa	4	1	2	0	7
5 MoSa	6	3	0	3	12
15 MoSa	5	1	1	0	7
50 MoSa	2	1	7	2	12

*Status epilepticus was defined as continuous tonic-clonic convulsions exceeding 2 min in duration.

†The number preceding each group indicates the dose of morphine used.

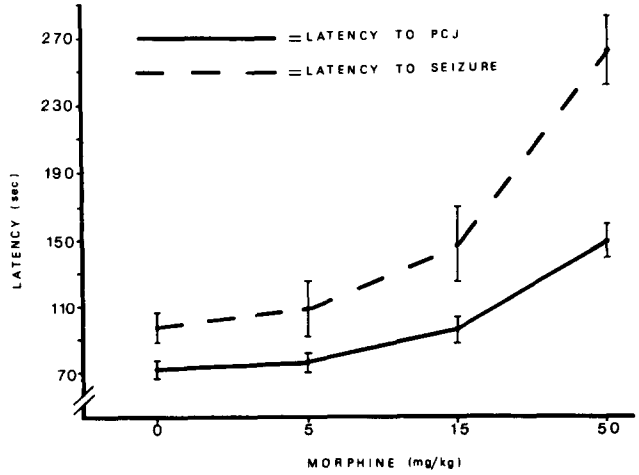

FIG. 2. The effects of morphine pretreatment on the latency to PCJ and the first PTZ-induced convulsion.

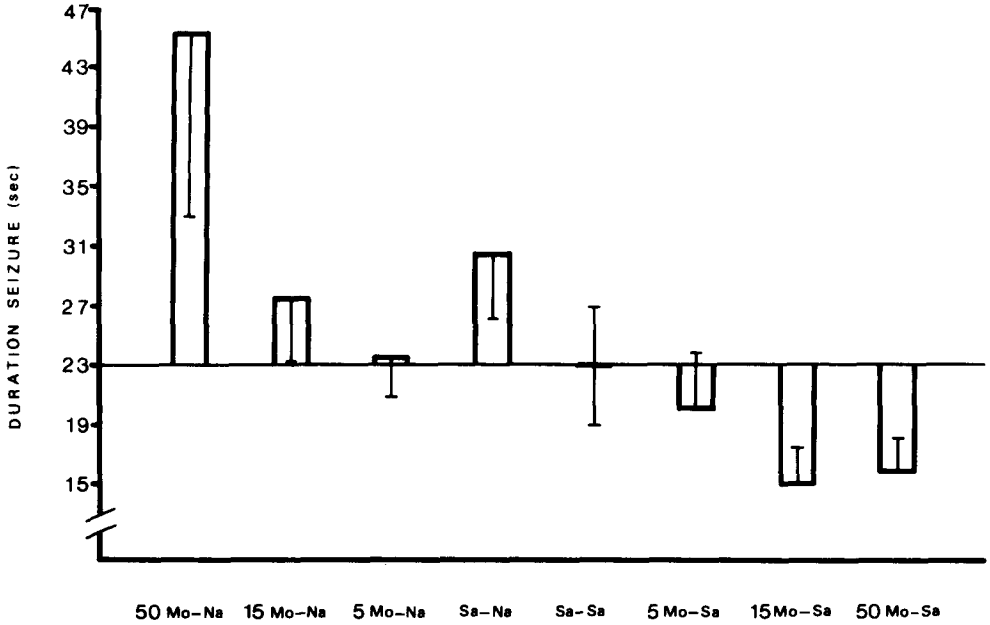

FIG. 3. The duration of the first PTZ-induced seizure in morphine—or morphine-naltrexone treated animals.

TABLE 2
PID DURATION FOR THE VARIOUS TREATMENT GROUPS

Group	Mean PID duration (sec)	SD	Group	Mean PID duration (sec)	SD
SaSa	47.2	± 19.0	SaNa	42.2	±35.6
5 MoSa*	302.8	± 45.4	5 MoNa	28.2	±17.0
15 MoSa*	398.0	±185.6	15 MoNa	47.8	±44.7
50 MoSa	—	—	50 MoNa	38.0	±13.6

*$p<0.05$ compared to all naltrexone-treated groups and group SaSa.

seizure was compared, $F(1,40)=17.93, p<0.01$. Animals that failed to show seizures or showed status epilepticus were not included in this anlaysis. A significant Dose×Treatment Interaction, $F(3,40)=3.3$, $p<0.05$, indicates that morphine tended to decrease the duration of convulsions whereas naltrexone injection following morphine resulted in a prolongation of seizures (Fig. 3). Although a clear cut dose related effect was not obtained it can be seen that pretreatment with the higher doses of morphine (15 and 50 MoSa, and also 15 and 50 MoNa) was more effective than pretreatment with the lower doses.

Post-ictal Depression (PID)

Table 2 summarizes the data concerning PID for all animals that showed only one PTZ-induced seizure. Because it was impossible to distinguish between the pre-ictal immobility and the PID of the animals of group 50 MoSa, these data have been excluded.

Multiple Seizures

Whereas the majority of animals in the present experiment displayed only one seizure during the 15 min following the injection of PTZ, a significantly higher incidence of seizures was observed in the animals of group MoSa when compared to those of SaSa ($p<0.01$). During these 15 min the average number of behavioral convulsions in the 50 MoSa group was 3.3 ± 1.9 compared to 1.1 ± 0.7 for group SaSa. Animals displaying multiple seizures or status epilepticus in the 50 MoSa group were treated either with naltrexone (5 mg/kg, n=5) or saline (1 ml/kg, n=4) 15 min after the PTZ injection (see Fig. 4).

Animals that received naltrexone significantly reduced seizure incidence over the next 15 min when compared to the 15 min before the naltrexone injection ($p<0.05$), and to the saline treated animals ($p<0.005$). The saline treated animals had significantly more seizures in the 15 min following the saline injection when compared to the 15 min prior to the saline injection ($p<0.05$). All animals injected with saline eventually died, whereas none of the naltrexone injected rats died.

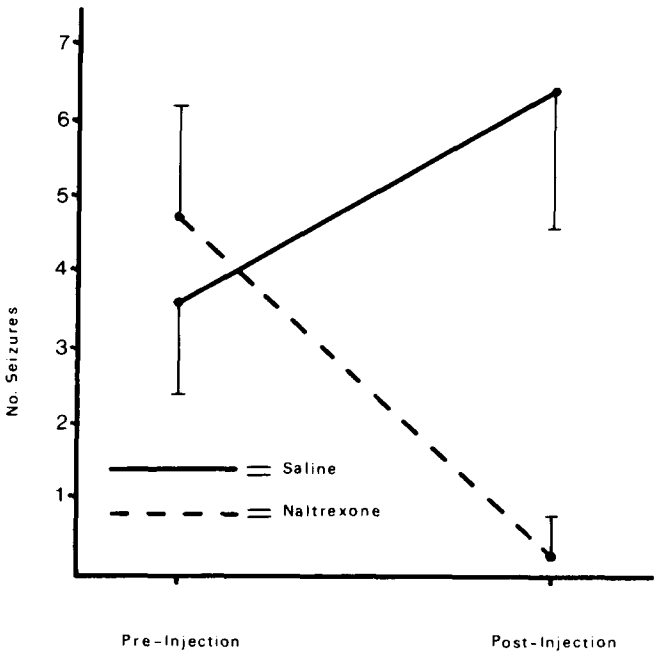

FIG. 4. The effects of naltrexone or saline on the incidence of seizures in animals showing multiple seizures following PTZ (Group 50 MoSa).

DISCUSSION

The results obtained in this experiment suggest that morphine may possess both pro- and anticonvulsant properties and that these could reflect different states of endogenous opioid systems preceeding and following convulsive events.

Examination of the data immediately following PTZ injections indicates that morphine possesses anticonvulsant properties. In the morphine-saline pretreated groups both the latency to the occurrence of the first preclonic jerk and the onset of behavioral convulsions following PTZ were increased in a dose related fashion with the highest dose of morphine used in this study producing a maximal effect. In addition, the duration of the first PTZ-induced seizure was shortened by morphine pretreatment, providing another demonstration of the anticonvulsant effect of morphine. Evidence for the opiate nature of these phenomena can be found in the fact that naltrexone pretreatment (morphine-naltrexone groups) blocked all the anticonvulsant effects of morphine. Moreover, when the duration of PTZ seizures is examined naltrexone pretreatment results in what appears to be a proconvulsant effect as indicated by the increased duration of seizures in these animals. Similar findings demonstrating the ability of morphine to delay pre-ictal and ictal events following PTZ administration in the rat have led Adler and his co-workers [1] to propose that morphine may possess anticonvulsant properties. On the other hand, Mannino and Wolf [14] have shown that morphine possesses proconvulsant effects when injected prior to PTZ in mice. The depressant effect of morphine in rats in contrast to its excitatory effects on mice has been used to explain these contra-

dictory effects on PTZ-induced seizures. Indeed, it is possible that such an approach may explain part of the results observed in this experiment. The dose-related anti-epileptic effect of morphine is also reflected in a dose-related decrease of locomotor activity. Inversely, naltrexone treatment (morphine-naltrexone) results in enhanced locomotor activity while a proconvulsant, albeit limited, effect is observed in animals belonging to these groups. If locomotor activity is an acceptable criterion for excitation then these data indicate that excitation per se may affect convulsive events.

The evidence discussed thus far concerning the anticonvulsant properties of morphine stand in marked contrast to previous studies demonstrating the convulsant effects of opiates [4, 8, 14]. However, the marked proconvulsant effects of morphine after the first convulsion are in line with the above-mentioned studies. Nine of the twelve animals receiving 50 mg/kg of morphine showed repeated seizures. Naltrexone effectively blocked the continuation of these seizures whereas in those animals receiving only the vehicle solution convulsions continued and in all cases led to the animal's death.

The drastic shift seen in morphine's characteristics from anticonvulsant pre-ictally to proconvulsant post-ictally indicates that convulsions can induce significant changes in the central nervous system. The repeated seizures observed in the morphine pretreated animals can be explained by assuming that the convulsive events caused a change such that morphine now potentiates the convulsant effects of PTZ. Alternatively, it is possible that following convulsions enhanced sensitivity to opiates occurs and that, as a result, the effective dose of morphine necessary for the elicitation of seizures is now reduced. The ability of naltrexone to block ongoing repeated seizures, although not constituting direct proof of this hypothesis, demonstrates that activity of opiates in this case is essential for the genesis of repeated convulsions.

Evidence for the development of increased sensitivity to morphine can also be seen in those animals receiving 5 or 15 mg/kg of morphine. Behavioral post-ictal depression was increased by 500% with cataleptic behavior accompanying this period resembling the effects of much higher doses of morphine in the drug naive animal. These effects are not due only to the sedating properties of morphine but are a result of a morphine-PTZ interaction. This can be seen from the fact that the PID seen in animals receiving 5 mg/kg of morphine is significantly higher than that of saline pretreated animals whereas their preseizure motility resembles or slightly exceeds that of controls. A similar potentiation of post-ictal behavioral depression has been observed in amygdaloid kindled animals [6], and electrographic recordings show that in such animals morphine dramatically increased post-ictal spiking in the amygdala and that this effect can be reversed by naloxone [6,13], thus again indicating that convulsions may enhance the efficacy of systemically applied opiates.

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