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Naloxone Enhances Epileptogenic and Behavioral Effects of Pentazocine in Rats

R. DIRKSEN,[1] A. M. L. COENEN* AND E. L. J. M. VAN LUIJTELAAR*[2]

*Institute for Anesthesiology and *Department of Psychology, University of Nijmegen, The Netherlands*

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DIRKSEN, R., A. M. L. COENEN AND E. L. J. M. VAN LUIJTELAAR. *Naloxone enhances epileptogenic and behavioral effects of pentazocine in rats*. PHARMACOL BIOCHEM BEHAV **39**(2) 415–420, 1991.—Eight groups of six rats were either injected with saline, pentazocine, naloxone, or a combination of pentazocine and naloxone. Studied were the effects on EEG and behavior. It was found that pentazocine induced epileptic seizures in a dose-dependent fashion. In addition, similar behavioral changes were present after all three doses of pentazocine. High doses of naloxone did not cause epilepsy and affected behavior only slightly. Seizures induced by pentazocine were not antagonized by the opiate antagonist naloxone, but were facilitated after the combination of a noneffective dose of pentazocine and a noneffective dose of naloxone. In addition, exploratory behavior was facilitated by the combination of pentazocine and naloxone. It seems that both an opiate and a nonopiate system are involved in this type of epilepsy and in this type of behavior.

Pentazocine Epilepsy Naloxone Rats EEG Behavior

PENTAZOCINE is a widely used and clinically effective benzomorphan-type opioid analgetic drug with both pro- and anticonvulsant effects in animals (5–7, 14). The bi-directional relationship of pentazocine with epilepsy is not unique for pentazocine but is shared with other opioid analgetics. The most extensively studied drug in this respect is morphine which also has pro- as well as anticonvulsant characteristics (7,13).

In a recent study towards the effects of IV pentazocine on nociception in rats (9), besides antinociceptive effects, behavioral effects such as jerks and forelimb and head clonus were also observed. Curiously, both the clonus and jerking responses were augmented by the opiate antagonist naloxone. In order to verify whether these behavioral manifestations seen after administration of pentazocine are genuinely epileptic, an EEG study is obligatory because any definition of epilepsy comprises an EEG as well as a behavioral element. Moreover, EEG-controlled studies are rare in this field, while epilepsy can only be confirmed if both EEG and clinical observations are made. One of the few studies in which an EEG was recorded after pentazocine administration in rats was performed by Colasanti and Khazan (5). Their study was aimed at describing the effects of pentazocine on the background EEG and it was found that another effect of opiates, the induction of large amplitude slow wave activity together with behavioral stupor, could be antagonized by naloxone. Furthermore, epilepsy was found only after 60 $mg \cdot kg^{-1}$ IP, that is substantially higher than the IV doses employed by Dirksen et al. (9). The purpose of the present EEG-controlled study was to investigate whether pentazocine indeed induces epilepsy and whether epileptic and behavioral effects are indeed not antagonizable by the opioid antagonist naloxone.

METHOD

Subjects

Forty-eight young male Wistar rats (age 4–5 months; body weight 330–410 g) from the outbred Cpb WU strain were used. They were purchased from the Harlan Institute (Zeist, The Netherlands). The animals were consistently kept at a 12:12 h light: dark regime with lights on at 0800 h. They were housed in macrolon cages and received tap water and standard rat chow ad lib. They were chronically provided with EEG (Plastic One, MS 333/2-A) and EMG electrodes (MS 303/71). The surgery was performed under pentobarbital anaesthesia (60 $mg \cdot kg^{-1}$ IP). Coordinates of the active electrodes were: A 2.0, L 3.5; A −6.0, L 4.0, with skull surface flat and bregma zero-zero. The reference electrode was set over the cerebellum. The EMG electrodes were subcutaneously placed onto the dorsal neck muscles. Three stainless steel screws were additionally attached to the skull and together with the electrode sets embedded in dental acrylic cement. The animals were allowed to recover for at least one week prior to the start of the experiment. One day before the actual experimental period the animals were placed in perspex recording cages (size $35 \times 30 \times 25$ cm) and adapted to the recording leads. EEG and EMG were recorded on an Elema-Schönander polygraph, paper speed 1.0 $cm \cdot sec^{-1}$, and frequencies between 1 and 70 Hz (EEG) and between 27 and 700 Hz (EMG) were allowed to pass.

Experimental Drugs

The drugs studied included: (±)-pentazocine-HCl (Sterling Winthrop), and (±)-naloxone-HCl (Diosynth, The Netherlands).

[1]Requests for reprints should be addressed to Dr. R. Dirksen, Institute for Anesthesiology, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.
[2]Dr. E. L. J. M. van Luijtelaar is supported by the Royal Dutch Academy of Sciences (KNAW).

In all rats, drugs and control fluid were injected intravenously directly in the tail vein in a volume of 1 ml·kg^{-1} body weight. Pentazocine-HCl was given to three groups of rats: they received IV 6, 9, and 12 mg·kg^{-1} pentazocine. Naloxone was given to two groups of rats: they received IV 8 mg·kg^{-1} and 16 mg·kg^{-1} naloxone.

Two groups received a combination of pentazocine and naloxone: 8 mg·kg^{-1} naloxone with either 6 (combination I) or 9 mg·kg^{-1} pentazocine (combination II). One group received normotonic saline. All solutions were freshly prepared on the day of the experiment. Each group consisted of six animals and all animals were used only once.

Procedure

Before drug or placebo administration, the baseline EEG was recorded during 30 min. During 15 min of this period, animals were closely observed from an adjacent room through a one-way window at a distance of less than one meter. These observations were also noted on the polygraph. The behavioral categories that were distinguished were: passive behavior (lying or sitting motionless), "automatic" behavior (grooming, eating, drinking) and "voluntary" behavior (mainly exploratory behavior and walking, rearing, leaning, digging) (9, 10, 27). Then animals were IV injected with a drug, combination of drugs, or a placebo. Thereafter, recordings were made during 90 min. Five minutes after injection the behavior of the animals was observed during 15 min and another two times with an interobservation interval of 15 min.

EEG and Statistical Analysis

Epileptic activity was identified by visual inspection of the EEG recordings. The dependent variables were the number of animals with seizures, the number of seizure periods, the latency to the first signs of epileptogenic activity (onset latency), the total time during which aberrant EEG activity was present (total time), and the latency for recovery (offset latency) from aberrant signs to a normally appearing, small amplitude high frequency EEG. The variable "number of animals with seizures" was analyzed with the Cochran test, the other epilepsy variables with the Kruskal-Wallis test (23).

The behavioral data obtained from the observation of the animals were analyzed with orthogonal trend analysis in order to justify the repeated measures taken (28): after the drug administration the behavior of the animals was observed three times. With trend analyses, the behavioral changes that occurred in the course of time are subdivided into parts of variation (linear, quadratic) while the sum of the parts of variation equals the total curvilinear variation. A positive linear trend means that the relationship between X (time) and a particular behavior (Y) increases ($y=ax$) when X increases, whereas a negative linear trend implies a decrease with time ($y=-ax$). A positive quadratic trend implies that the relationship between X and Y can also be described with a parabolic function $y=bx^2$, a negative quadratic trend with $y=-bx^2$. The linear and quadratic trends are independent from the general mean, the mean over the three time points. With a simple one factor (doses) ANOVA an effect of the doses on the general mean and trend components (a and b's) caused by the drugs could be determined, if necessary subsequent post hocs (Duncan's, $p<0.05$) determined differences among groups. In detail, dose dependency for pentazocine was tested by comparing saline with the three pentazocine groups and dose dependency for naloxone with a comparison between saline and the two naloxone groups. The effects of the combinations were tested in two separate ANOVA's: in the first analysis saline, 6 mg·kg^{-1} pentazocine, 8 mg·kg^{-1} naloxone, and combination I were compared; in the second analysis saline, 9 mg·kg^{-1} pentazocine, 8 mg·kg^{-1} naloxone, and combination II.

RESULTS

An example of a complete pentazocine-induced seizure is shown in Fig. 1. Shortly after the injection of 12 mg·kg^{-1} pentazocine, the seizure started with forelimbs and head jerks accompanied by large amplitude polyspikes. This was followed by a period of 9–10 Hz spike-waves with minor vibrissal twitching and facial jerks. Then again, polyspikes of a decreasing frequency occurred with head and forelimb jerks which were followed by a small amplitude fast EEG. During the latter period, animals remained motionless. Sometimes again single small polyspikes were shown and after 12 mg·kg^{-1} pentazocine and also after combination II, a second sequence of events was shown, which ended with a period of iso-electric activity. After the disappearance of the aberrant EEG activity, animals slowly regained their normal behavioral repertoire.

Pentazocine and Epileptic Activity

Before injection, no aberrant signs were present. Epileptic activity was present in none of the animals after saline and also in none after 6 mg·kg^{-1} pentazocine; in 3 animals after 9 mg·kg^{-1}, and in 5 rats after 12 mg·kg^{-1} pentazocine. As mentioned before, group size was always $n=6$. The Cochran test showed that these results were not due to chance alone ($p<0.01$). Likewise, the onset latency, the mean number of seizure periods, the total time, and the offset latency were different for these four groups (Kruskal-Wallis, all four ps<0.01). The results are depicted in Table 1.

Effects of Pentazocine on Behavior

Before injection, there were no differences between the saline and the three pentazocine groups. The trend analysis and the post hoc tests revealed that the general mean of passive behavior was less after pentazocine, $F_{gen.\ mean}(3,20)=7.52$, $p<0.01$: there were no differences between the three pentazocine groups but all groups were significantly lower than the saline group. A significant linear trend was found for automatic behavior, $F_{lin}(3,20)=11.00$, $p<0.001$, explaining 97% of the curvilinear variation. The three pentazocine groups showed an identical positive linear trend which was absent in the placebo group.

Voluntary behavior was enhanced after pentazocine administration as was shown by an increase in the general mean, $F_{gen.\ mean}(3,20)=12.65$, $p<0.001$: the three pentazocine groups were all higher than compared to saline. Also a drug effect was noticed on the linear and quadratic trend, $F_{lin}(3,20)=6.18$, $p<0.01$; $F_{quad}(3,20)=3.35$, $p<0.05$, explaining 81 and 19% of the curvilinear variation respectively: all three pentazocine groups showed a similar and larger negative linear trend during the three observation periods compared to placebo. The quadratic trend was larger after 9 and 12 mg·kg^{-1} than after 6 mg·kg^{-1} pentazocine.

Naloxone, Epileptic Activity and Behavior

Naloxone did not induce epileptic phenomena. A drug effect was found on passive behavior, $F_{quad}(2,15)=3.80$, $p<0.05$ (27%). This trend was larger for 8 mg·kg^{-1} naloxone compared to saline. On voluntary behavior a linear trend difference was induced by naloxone, $F_{lin}(2,15)=6.55$, $p<0.01$ (81%): the negative trend after 16 mg·kg^{-1} naloxone was larger than that after saline.

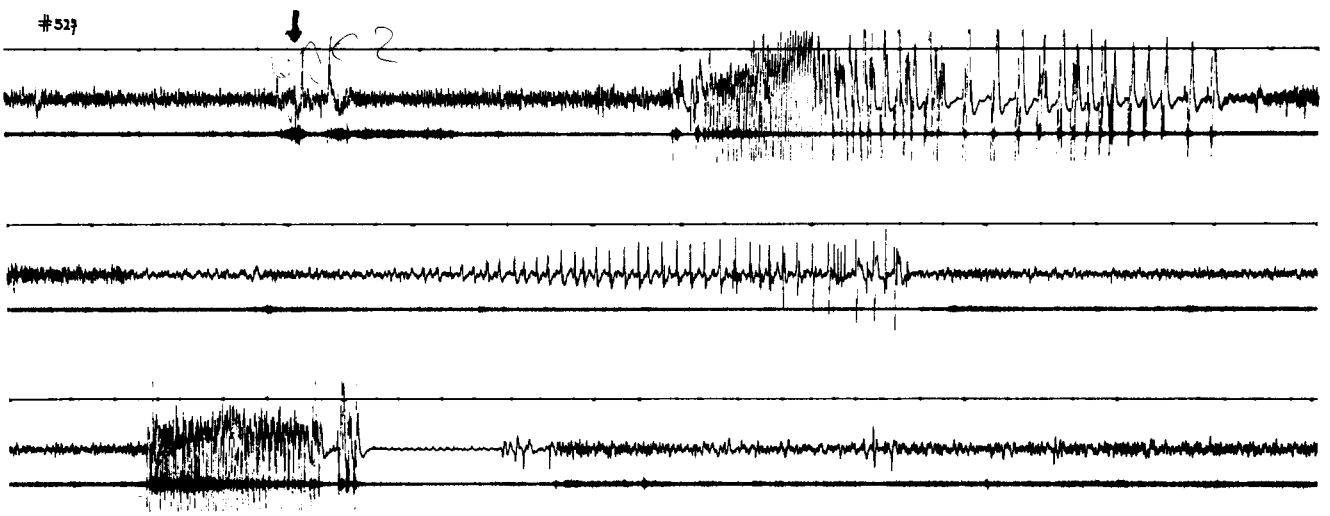

FIG. 1. Example of three minutes of EEG and EMG recordings after administration of 12 mg·kg^{-1} pentazocine. The arrow in the upper trace indicates the IV injection of pentazocine. The EEG remains normal until about half the upper trace, then two incidental myoclonic jerks can be noticed in the EMG, followed by about four second lasting 2–3 Hz jerks with large amplitude polyspikes in the EEG. This is followed by 9–11 Hz spike-wave discharges, while the animals remains almost motionless. Then the jerks reappear together with polyspikes. The frequency of spikes and jerks decreases from 3 to 0.5 Hz. The last part of the upper and the beginning of the second EEG trace is characterized by low amplitude and high frequencies in the EEG. In the middle of the second trace polyspikes appear, the amplitude of the spikes increases with time while the animal remains motionless. They disappear suddenly, then the EEG remains relatively small. At the bottom trace, a second period of seizures is noticed, followed by a short period of iso-electric activity. Towards the end of this trace the EEG normalizes slowly.

Combination I and II: Epilepsy

None of the animals showed convulsions after 6 mg·kg^{-1} pentazocine, however, when 6 mg·kg^{-1} pentazocine was combined with 8 mg·kg^{-1} naloxone, 3 of the 6 rats showed full blown epileptic seizures. The Kruskal-Wallis test showed differences between saline, naloxone, pentazocine and combination I for the mean number of seizure periods, the onset and offset latency, and the total time (all $ps<0.05$). After the combination the onset latency was shorter, the offset latency and the total time were enhanced.

In order to establish a dose-effect relationship, 8 mg·kg^{-1} naloxone was also combined with 9 mg·kg^{-1} pentazocine. Now all 6 animals showed the full blown seizures. The Kruskal-Wallis test showed differences between saline, naloxone, pentazocine, and combination II for all epilepsy variables (all $ps<0.01$).

TABLE 1

OVERVIEW OF EFFECTS OF PENTAZOCINE AND NALOXONE ON THE EEG (MEANS AND SEM ARE GIVEN)

		Parameters of Epilepsy			
Drugs	n	Onset Latency	Total Time	Offset Latency	Number of Seizures
Saline	0	—	0	—	0
Pentazocine 6 mg·kg^{-1}	0	—	0	—	0
Pentazocine 9 mg·kg^{-1}	3	22 ± 12	38 ± 17	40 ± 18	0.5 ± 0.2
Pentazocine 12 mg·kg^{-1}	5	12 ± 3	87 ± 24	250 ± 68	3.5 ± 0.9
Naloxone 8 mg·kg^{-1}	0	—	0	—	0
Naloxone 16 mg·kg^{-1}	0	—	0	—	0
Pentazocine 6 mg·kg^{-1}	0	—	0	—	0
Combination I	3	16 ± 7	37 ± 17	59 ± 30	0.7 ± 0.3
Pentazocine 9 mg·kg^{-1}	3	22 ± 12	38 ± 17	40 ± 18	0.5 ± 0.2
Combination II	6	26 ± 4	80 ± 8	161 ± 19	2.3 ± 0.2

The number of animals which showed epilepsy is indicated by n, onset latency is the latency in s until the first signs of aberrant EEG activity appear, total time is the sum of all EEG parts with aberrant EEG activity in s, offset latency is the latency in s until the normal EEG returns, number of seizures is the mean number of seizure periods after a single injection. A — indicates that there was no epilepsy (for the statistical analyses a latency of 90 s was then taken, the latencies were also ln transformed).

TABLE 2

OVERVIEW OF THE EFFECTS OF 6 AND 9 mg·kg^{-1} PENTAZOCINE AND THE ANTAGONISM BY 8 mg·kg^{-1} NALOXONE ON THE GENERAL MEAN (M) AND LINEAR (L) TREND OF PASSIVE, AUTOMATIC AND VOLUNTARY BEHAVIOR

Drug(s)	Passive		Automatic		Voluntary	
	M	L	M	L	M	L
Pentazocine 6 mg·kg^{-1}	s.	n.s.	n.s.	s.	s.	s
Combination I	Ant			Ant	Ant	—
Pentazocine 9 mg·kg^{-1}	s.	n.s.	n.s.	s.	s.	s.
Combination II	Ant			Ant	—	Pot

Significant (s.) and nonsignificant (n.s.) pentazocine effects (different from saline) are indicated in the first row. If naloxone antagonizes the pentazocine effect, this is indicated with Ant; if naloxone fails to block the pentazocine effect, this is indicated by —; if naloxone aggravates the pentazocine effect, this is indicated by Pot.

Subsequent tests (Wilcoxon 2-sample test) showed that the mean number of seizures ($p<0.01$), the onset ($p<0.05$) and the offset latency ($p<0.01$) were all higher for combination II compared to 9 mg·kg^{-1} pentazocine alone. Additional comparisons between combination I and II showed more seizures ($p<0.01$), a shorter onset latency ($p<0.05$) and a longer offset latency ($p<0.02$) after combination II.

Combination I and II: Effects on Behavior

The injection of combination I affected both passive, automatic, and voluntary behavior. Drug effects were found for the general mean, $F_{gen.\ mean}(3,20)=15.34$, $p<0.001$, and the linear trend, $F_{lin}(3,20)=4.10$, $p<0.05$ (58%), of passive behavior, the linear trend, $F_{lin}(3,20)=10.54$, $p<0.001$ (82%), of automatic behavior and the general mean, $F_{gen.\ mean}(3,20)=25.61$, $p<0.0001$, and linear trend, $F_{lin}(3,20)=8.10$, $p<0.001$ (88%), of voluntary behavior. In Table 2 is indicated whether 6 mg·kg^{-1} pentazocine was significantly different from saline. This table also indicates whether naloxone antagonized the effects of pentazocine. Almost all significant pentazocine effects were antagonized by naloxone: the general mean of passive and voluntary behavior and the linear trend of automatic behavior. However, there was an exception. There was no difference on the linear trend of voluntary behavior between combination I and 6 mg·kg^{-1} pentazocine, indicating that naloxone did not counteract this pentazocine effect.

The injection of combination II also affected passive, automatic, and voluntary behavior. Drug effects were found for the the general mean, $F_{gen.\ mean}(3,20)=6.23$, $p<0.01$, and the linear trend, $F_{lin}(3,20)=7.22$, $p<0.001$ (77%), of passive behavior, the general mean, $F_{gen.\ mean}(3,20)=3.12$, $p<0.05$, and linear, $F_{lin}(3,20)=13.12$, $p<0.001$ (83%), trend of automatic behavior and the general mean, $F_{gen.\ mean}(3,20)=16.42$, $p<0.0001$, and linear trend, $F_{lin}(3,20)=27.03$, $p<0.0001$ (88%), of voluntary behavior. In Table 2 is indicated whether 9 mg·kg^{-1} pentazocine was significantly different from saline.

In agreement with the results obtained after the administration of combination I, not all pentazocine effects were antagonized by naloxone: only the general mean of passive and automatic behavior and the linear trend of automatic behavior. The linear trend of voluntary behavior showed a completely different picture: now the effects of combination II were significantly larger ($p<0.05$) that those of 9 mg·kg^{-1} pentazocine alone, i.e., the effects of pentazocine were potentiated by naloxone. Also of interest is that the general mean of voluntary behavior of combination II is not different from that of 9 mg·kg^{-1} pentazocine, which indicates that naloxone did not block the mean of voluntary behavior as well.

DISCUSSION

A characteristic pattern of unambiguous EEG and clinical signs of epilepsy were noticed within 30 seconds after the administration of 9 and 12 mg·kg^{-1} pentazocine. The type and nature of the aberrant EEG activity resembles the effects obtained after morphine administration (11,12). EEG and EMG tracings revealed that the EEG manifestations extended beyond the clinical signs of epilepsy: head and forelimb clonus and jerks were present only during the large amplitude polyspikes. No gross overt clinical signs were visible during the spike-wave-like pattern and during iso-electric activity. The animal sat motionless during the spike-wave discharges; only vibrissal twitching was noticed while the nuchal EMG showed an increase in muscle tone. It can be concluded that pentazocine induces epilepsy and that the clinical signs are an underestimation of the duration of the aberrant EEG activity.

The epilepsy-inducing effects of pentazocine are related to the dose, as evidenced by the number of animals showing convulsions, the onset time, the number of convulsive periods and the time till the disappearance of the aberrant EEG signs. The proconvulsive effects of (+)-pentazocine were earlier reported in chemically induced epilepsy by Cowan et al. (6). They found that in rats pentazocine reduced the threshold for flurothyl-induced convulsions and that (+)-pentazocine was more potent than (−)-pentazocine as a proconvulsant. Tortella et al. (26) reported an anti-epileptic effect of pentazocine in rats measured by an increase in the threshold for flurothyl-induced convulsions after ICV injection, but after SC administration a proconvulsive effect. This seems in agreement with the present proconvulsant effect after IV administration. A single IV injection of naloxone (8 or 16 mg·kg^{-1}) was without proconvulsive effects in our hands. This is in agreement with earlier findings of others (5,26).

Naloxone did not antagonize the proconvulsive effects of pentazocine. Moreover, all epilepsy indices were aggravated after the coinjections. These results are in contrast with those which have been obtained after morphine administration: naloxone antagonizes the ability of morphine to lower the threshold for seizures induced with pentylenetetrazol or flurothyl in rats (6,12).

Pentazocine also affects the spontaneous behavior of the rats in their home cage; all three behavioral categories, passive, automatic and voluntary behavior, were altered. A decrease in passive behavior was found and a minimum immediately after injection of automatic behavior was followed by a steady increase, expressed by a positive linear trend. Finally, a negative trend after the drug was found for voluntary behavior. There were no clear differences between the three pentazocine groups, the only difference noticed was that from placebo. Although this experiment was aimed to establish the effects of the combined treatment on epilepsy and not aimed to obtain a dose-effect relationship between pentazocine and behavior, it can be inferred that the used dosages were too high to establish a dose-effect relationship for behavior. Since dose dependency was suggested for the epilepsy-inducing effects of pentazocine, it seems that the behavior is already influenced by lower doses than those required to cause epilepsy.

Naloxone is without clear behavioral effects, which is in

agreement with what is generally reported [e.g., (15)]. However, the linear trend of voluntary behavior is larger after the larger dose than after saline, suggesting a genuine effect of naloxone. The significant effects of the low dose of pentazocine on behavior were antagonized, however, not those on the linear trend of voluntary behavior. In the comparison for this variable, there were no differences between naloxone with the low doses of pentazocine compared to pentazocine alone. After combination II, naloxone potentiated the effects of pentazocine on the linear trend of voluntary behavior, while the general mean was unaffected after the combination. This shows that passive and automatic behavior are under the influence of an opioid system, fulfilling the condition agonized by an agonist and blocked by an antagonist. In contrast, voluntary behavior is changed by pentazocine but not antagonized by naloxone; this latter result casts doubt on the role of the opioid system alone on voluntary behavior.

It can be concluded that pentazocine affects the spontaneously occurring behavior of rats in their home cage, that naloxone itself has no or only a small effect, and that after the combination of pentazocine and naloxone only passive and automatic, but not voluntary, behavior is antagonized. In combination with naloxone, pentazocine has stronger effects on voluntary behavior. These latter effects on behavior are at least partially in agreement with the effects on epilepsy obtained after the administration of both combinations, which also results in an aggravation of epilepsy. These agonist-antagonist interactions of the combinations are surprising; however, they are in agreement with the outcomes of a recent study of Dirksen et al. (10). In their experiment, an ineffective dose of pentazocine was also combined with naloxone. They found an increase in the antinociceptive effects in the hot-plate test after the combination. Also naloxone enhanced the analgetic effect of systemic pentazocine (19). It seems, therefore, that at least three effects of pentazocine, the analgesic response, the induction of epilepsy, and its effect on voluntary behavior, are not antagonized by naloxone, but rather enhanced.

The agonistic effects of pentazocine and the partial potentiation by naloxone on epilepsy and voluntary behavior are difficult to explain with one single mechanism. Therefore, two mechanisms have been proposed, an opioid and a nonopioid system (13). The earlier finding of an effect of (−)-pentazocine (6) and the simple fact that a dose-effect relationship of pentazocine has been found does underscore the involvement of an opioid receptor, although the lack of specificity of pentazocine for the various opioid receptors systems does not allow firm statements about the receptor subtypes which are involved. If only the opioid system would be involved, naloxone should block the effects of pentazocine but in the present study an opposite effect is found for the epilepsy variables and for the linear trend of voluntary behavior.

Although many neurohumoral systems are involved in the etiology of epilepsy, it is without doubt that the inhibitory GABA-ergic system is involved in the regulating mechanisms of convulsive epilepsy (13,16). There are several indications for this view. First of all, it is well known that GABA antagonists induce convulsive epilepsy [e.g., (20)]. Furthermore, morphine potentiates seizures induced by GABA antagonists (11). The similarity of GABA antagonists and opiates in inducing convulsions might point in the direction of the view that opiates reduce GABA-ergic transmission. Sagratella and Massotti (22) and Dingledine et al. (8) described that doses of naloxone, similar to those employed by us, act as GABA-antagonists. Jacquet et al. (18) reported that both morphine and naloxone reverse the inhibitory effect of GABA on the binding of ^{35}S-TBPS, a label for the convulsant site of the $GABA_A$ receptor. Preliminary results from our laboratory confirmed and extended this observation for pentazocine: morphine, naloxone and pentazocine all reverse the inhibitory effect of GABA on ^{3}H-TBOB binding (van Rijn et al., in preparation). Squires and Seaderup (24) suggested that reversal of the inhibitory effect of GABA on the binding of TBOB and TBPS matches the seizure liability of a compound. This all strongly suggests that the nonopioid mode of action of pentazocine and naloxone is accomplished by an inhibitory action on the $GABA_A$-receptor complex.

Several reports have appeared with respect to the appearance of serious signs of epilepsy after opiates, e.g., fentanyl, sufentanil, or alfentanil (2, 21, 25). Incidental reports on seizures associated with high dose of pentazocine appeared way back (1,17). Czuczwar and Frey (7) also point towards the potential hazard of pentazocine in "seizure-prone" subjects. Their warning was based on the aggravation or potentiation of pentetrazole-induced epilepsy by pentazocine. It the present study it is shown that when normal Wistar rats show behavioral and clinical signs of opiate-induced epilepsy, these phenomena are enhanced by naloxone. This strongly suggests that seizures occurring after pentazocine overdose should not be controlled by naloxone, perhaps by anticonvulsants.

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