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Opioid Inhibition of Kainic Acid-Induced Scratching: Mediation by Mu and Sigma But Not Delta and Kappa Receptors

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KELLSTEIN, D. E., R. C. COGHILL, H. FRENK, D. F. BOSSUT AND D. J. MAYER. *Opioid inhibition of kainic acid-induced scratching: Mediation by mu and sigma but not delta and kappa receptors.* PHARMACOL BIOCHEM BEHAV **35**(1) 1–5, 1990.—Scratching induced by intrathecal (IT) administration of kainic acid (0.5 nmol) to rats was inhibited by IT pretreatment with the selective mu agonists levorphanol (30 and 90 nmol), [D-Ala^2,N-Met-Phe^4,Gly^5-ol]-enkephalin (DAGO, 0.4 and 1.1 nmol), or morphine (90 nmol), the mixed mu-delta agonist [D-Ala^2,D-Leu^5]-enkephalinamide (DADLE, 10 and 30 nmol), or the sigma/phencyclidine (PCP) agonists dextrorphan (90 nmol) or (+)-N-allyl-N-normetazocine ([+]-NAM, 90 nmol). The kappa agonists dynorphin (1.1 nmol) and ethylketocyclazocine (EKC, 90 nmol) had no significant effect, nor did the selective delta agonist [D-Pen^2,D-Pen^5]-enkephalinamide (DPDPE, 90 nmol). The nonopioids (+)-3-(3-hydroxyphenyl)-N-(1-propyl)piperidine ([+]-3-PPP, 90 nmol) and PCP (90 nmol), selective for sigma and PCP sites, respectively, both antagonized kainic-induced scratching. Levorphanol- and DADLE-induced attenuation of scratching was partially antagonized by naltrexone. These findings suggest that opioid inhibition of kainic acid-induced scratching is mediated by classical mu receptors as well as sigma and PCP sites.

Opioids Kainic acid Intrathecal Opioid receptors Sigma receptors PCP receptors Scratching Naltrexone

INTRATHECAL (IT) administration of a wide variety of generally neuroexcitatory compounds to rodents elicits a behavioral syndrome characterized by hindlimb scratching, caudally directed biting or licking, and sometimes vocalization and myoclonic twitching. Examples of such compounds include substance P (5, 6, 9, 10, 16, 17), capsaicin (16), L-glutamic acid (1, 9, 10), picrotoxin (3, 9, 10), strychnine (4–6, 9, 10), N-methyl-D-aspartate (NMDA) (1,2) and kainic acid (2, 5, 6, 9, 10, 18). A subsequent study in our laboratory using the rat indicated that IT morphine enhanced hindlimb scratching induced by substance P, but inhibited this response when induced by strychnine or kainic acid (5). The present study attempted to elucidate the opioid receptor subtype(s) mediating attenuation of kainic acid-induced scratching, and to determine if this inhibition could be blocked by the opioid antagonist naltrexone.

METHOD

Animals

Adult male Sprague-Dawley rats (Hilltop) weighing 400–450 g at the time of surgery were used in all experiments. Animals were individually housed in stainless steel cages under a 12-hr light cycle (lights on from 07.00 to 19.00 hr). Food and laboratory chow were available ad lib.

Surgery

Animals were implanted with IT catheters while under sodium pentobarbital (50 mg/kg, IP) anesthesia. A segment of polyethylene tubing (PE 10) filled with 0.4% gentamicin solution was inserted through a small incision in the atlanto-occipital membrane and gently advanced 8.5 cm caudally to the rostral edge of the lumbosacral enlargement. The catheter was secured to a skull screw with dental acrylic cement and the rostral end was sealed with a sterilized segment of 30 gauge wire. Immediately after surgery, animals received penicillin G suspension (100,000 units/kg, IM) and were allowed to recover for five days.

Drugs and IT Injection Technique

Opioids were selected based on their relative affinity to

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receptor subtypes. Mu agonists used were levorphanol (30 and 90 nmol) (23,32), morphine (90 nmol) (23,24), and [D-Ala^2,N-Met-Phe^4,Gly^5-ol]-enkephalin (DAGO, 0.4 and 1.1 nmol) (19,23). The mixed mu-delta agonist [D-Ala^2,D-Leu^5]-enkephalinamide (DADLE, 10 and 30 nmol) (7,23), and the more specific delta agonist [D-Pen^2,D-Pen^5]-enkephalinamide (DPDPE, 90 nmol) (23,25) were also chosen. Dynorphin (1.1 nmol) (15) and ethylketocyclazocine (EKC, 90 nmol) (19, 23, 27) served as kappa agonists, while dextrorphan (90 nmol) was selected as the dextrorotary control for its stereoisomer, levorphanol (28). The doses employed correspond to the effective dose of morphine (90 nmol) obtained in a previous study (5), except when limited by hindlimb flaccidity or paralysis (DADLE, DAGO, dynorphin), in which case the highest $\log_3$ dose not producing motor effects was used. All opioids were dissolved in sterile 0.9% saline and injected IT in 10 μl.

A second experiment investigated the effects of compounds with varying degrees of affinity for the nonopioid sigma and phencyclidine (PCP) binding sites. (+)-3-(3-hydroxyphenyl)-N-(1-propyl)piperidine ([+]-3-PPP, 90 nmol) was employed as a specific sigma ligand (8, 11, 12, 20–22), (+)-N-allyl-N-normetazocine ([+]-NAM, 90 nmol) was selected as a mixed sigma/PCP agonist with greater affinity for sigma than PCP sites (8, 11, 21), and PCP (90 nmol) was used as a selective PCP ligand (8,11). Dextrorphan (90 nmol), a mixed sigma/PCP ligand with greater affinity for PCP than sigma receptors (8), was also included in this study.

To minimize handling, animals were placed in transparent polycarbonate restrainer tubes during injection. Restrainers were slotted on the dorsal surface to allow access to IT catheters and on the ventral surface to permit intraperitoneal injections. In the first experiment, all animals were pretreated with systemic saline (1 ml/kg, IP) so that some groups (saline, levorphanol 90 nmol, DADLE 10 nmol) could be used as controls in the third study. Ten min later, either an opioid or equivolume (10 μl) saline was injected IT; following an additional ten min, IT kainic acid (0.5 nmol in 10 μl saline) was administered. In the second experiment, sigma/PCP ligands or saline were injected IT followed in ten min by IT kainic acid. Each IT injection was performed over 10–15 sec using a Hamilton 50 μl microsyringe and followed by 10 μl (void volume of catheters) of saline to flush the drug into the subarachnoid space.

In the third study, animals were pretreated systemically with naltrexone (30 mg/kg, IP) or saline (1 ml/kg, IP). Ten min later, either IT saline, levorphanol (90 nmol) or DADLE (10 nmol) was injected followed in 10 min by IT kainic acid as above.

Behavioral Observations

Immediately following kainic acid injection, animals were removed from restrainers and placed in a plastic box (47 × 25 × 20 cm) open at the top. They were observed for 10 min postinjection for spontanously occurring hindlimb scratching of the flanks and caudally directed biting and licking. The total number of scratches and bites/licks which occurred during the 10-min observation interval was recorded.

Statistics

Due to the nonparametric nature of the data, treatment groups were compared using the Mann-Whitney U-test, and median number of events with ranges are indicated in the figures. With the exception of morphine, all groups were tested using two-tailed criteria. Since previous studies (5) indicated that morphine decreased kainic acid-induced scratching, one-tailed comparison was employed for this group. Differences were considered to be significant at the 5% level ($p<0.05$).

RESULTS

Intrathecal injection of kainic acid resulted in bilateral hindlimb scratching of the flanks and caudally directed biting or licking, although the incidence of scratching was much higher than biting/licking. The median number of scratches and bites/licks over the ten-minute observation period was 234 (Fig. 1) and 13 (Table 1), respectively.

Opioid Inhibition of Kainic Acid-Induced Scratching

Pretreatment with the mu agonists levorphanol (30 and 90 nmol) or DAGO (0.4 and 1.1 nmol) significantly reduced kainic acid-induced scratching in a dose-related manner (Fig. 1); biting/licking was also antagonized (Table 1). Morphine (90 nmol) pretreatment also reduced scratching (Fig. 1), but not biting/licking (Table 1).

The mixed mu-delta agonist DADLE (10 and 30 nmol) reliably attenuated scratching in a dose-related manner (Fig. 1); only the higher dose inhibited biting (Table 1). Inhibition of scratching by the selective delta agonist DPDPE (90 nmol) was not significant (Fig. 1), although biting was significantly reduced (Table 1).

Neither kappa agonist reliably inhibited scratching; dynorphin (1.1 nmol) pretreatment slightly increased the number of scratches, whereas EKC (90 nmol) reduction of this behavior was not significant (Fig. 1). Biting was slightly enhanced by the former, but completely abolished by the latter (Table 1).

Pretreatment with the PCP/sigma ligand dextrorphan (90 nmol) reliably reduced kainic acid-induced scratching (Fig. 1) but not biting (Table 1).

Sigma/PCP Inhibition of Kainic Acid-Induced Scratching

All of the drugs active at sigma and/or PCP receptors ([+]-3-PPP, [+]-NAM, dextrorphan, PCP) significantly reduced kainic-induced scratching when administered at 90 nmol (Fig. 2). Only (+)-3-PPP reliably reduced the number of bites/licks (not shown).

Naltrexone Antagonism of Opioid Inhibition

Naltrexone (30 mg/kg, IP) alone had no effect upon kainic acid-induced scratching compared to saline pretreatment (Fig. 3). The median values for scratches were 224 and 212 for saline and naltrexone, respectively; biting was similarly unaltered (respective medians 13 and 11). After naltrexone pretreatment, the number of kainic acid-induced scratches following levorphanol (90 nmol) was significantly greater than that observed after saline + levorphanol, but significantly less than that obtained after saline + saline (Fig. 3), i.e., naltrexone partially blocked levorphanol-induced attenuation of scratching. Levorphanol inhibition of biting behavior was slightly, but not significantly blocked by naltrexone pretreatment (respective medians 0 and 8).

Naltrexone had an identical effect on DADLE (10 nmol)-induced inhibition of scratching: partial antagonism. Scratching following naltrexone + DADLE was significantly greater than after saline + DADLE, but significantly less than after saline + saline (Fig. 3). As with levorphanol, naltrexone blockade of DADLE-induced antagonism of biting/licking was not significant (median increased from 6.5 without naltrexone to 12.5 with naltrexone).

DISCUSSION

In agreement with previous results, the present study demon-

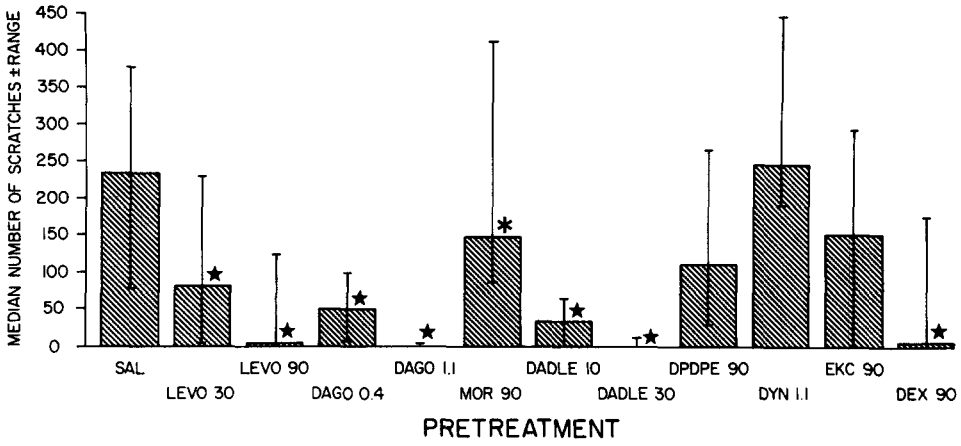

FIG. 1. Opioid inhibition of kainic acid-induced scratching. All rats received saline (SAL; 1 ml/kg, IP) followed in 10 min by IT injection of either SAL [10 μl (N = 11)], levorphanol [LEVO; 30 nmol (N = 12) or 90 nmol (N = 11)], DAGO [0.4 nmol (N = 6) or 1.1 nmol (N = 5)], morphine [MOR; 90 nmol (N = 8)], DADLE [10 or 30 nmol (N = 6)], DPDPE [90 nmol (N = 6)], dynorphin [DYN; 1.1 nmol (N = 6)], EKC [90 nmol (N = 6)] or dextrorphan [DEX; 90 nmol (N = 5)]. Ten min later, kainic acid (0.5 nmol, IT) was injected and scratches were counted for 10 min. *$p<0.05$, ⋆$p<0.005$ compared to SAL using Mann-Whitney U-test.

strates that IT injection of kainic acid (0.5 nmol) produces bilateral hindlimb scratching of the flanks and, to a lesser extent, biting/licking of the haunches and hindpaws (2, 5, 6, 9, 10). This dose of kainic acid does not induce vocalization and myoclonic twitching, although a higher dose (0.9 nmol) does (10).

The exact mechanism by which kainic acid induces scratching is not known, but previous findings that 1) spinalization of rats does not inhibit this behavior (5), and 2) pretreatment with anticonvulsants (valproic acid or chlordiazepoxide) reduces kainic acid-induced scratching (9) indicate that this behavior is spinally mediated and probably attributable to proconvulsant activity of kainic acid.

Kainic acid-induced spinal excitation may also initiate biting/licking, since this behavior frequently follows a scratching episode (10) and is inhibited by anticonvulsants (9). In the present study, six treatments which significantly inhibited scratching also antagonized biting/licking (Table 1), suggesting that the behaviors may be linked. Several treatments, however, attenuated one behavior without affecting the other, suggesting that 1) biting/licking may occur independently of scratching and 2) the ascending pathways mediating the former may employ different neuromodulators than the local spinal circuitry underlying the latter.

In agreement with results obtained previously (5), morphine (90 nmol) inhibited kainic acid-induced scratching, although to a lesser extent than levorphanol or DAGO, both of which significantly antagonized this behavior in a dose-related manner. Levor-

TABLE 1

OPIOID INHIBITION OF KAINIC ACID-INDUCED BITING/LICKING AND COMPARISON TO INHIBITION OF SCRATCHING

Opioid	Dose (nmol)	N	Median Number of Bites/Licks	Significance	Significant Effect on Scratch
None (saline)	—	11	13	—	—
Levorphanol	30	12	1	$p<0.05$	$p<0.005$
Levorphanol	90	11	0	$p<0.01$	$p<0.005$
DAGO	0.4	6	0	$p<0.01$	$p<0.005$
DAGO	1.1	5	0	$p<0.005$	$p<0.005$
Morphine	90	8	10	No (one-tailed)	$p<0.05$ (one-tailed)
DADLE	10	6	6.5	No	$p<0.005$
DADLE	30	6	0	$p<0.05$	$p<0.005$
DPDPE	90	6	3.5	$p<0.05$	No
Dynorphin	1.1	6	19.5	No	No
EKC	90	6	0	$p<0.001$	No
Dextrorphan	90	5	0	No	$p<0.005$

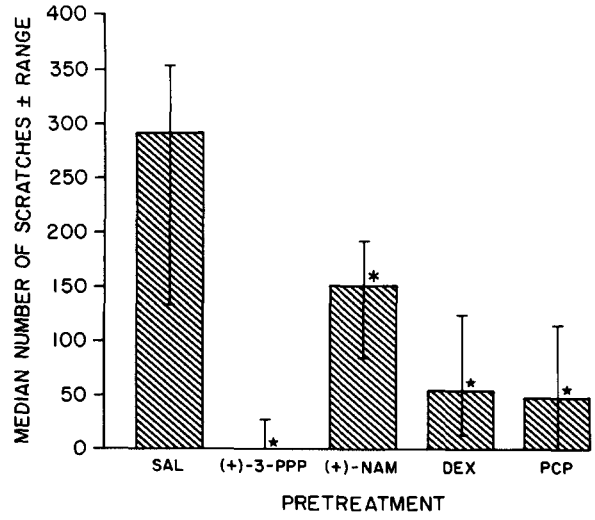

FIG. 2. Inhibition of kainic acid-induced scratching by drugs active at sigma and/or PCP receptors. Rats were injected IT with either SAL (10 μl), (+)-3-PPP (90 nmol), (+)-NAM (90 nmol), dextrorphan (DEX; 90 nmol) or PCP (90 nmol). Ten min later, kainic acid (0.5 nmol, IT) was injected and scratches were counted for 10 min. N = 6 for all groups. *$p<0.05$, ⋆$p<0.005$ compared to SAL using Mann-Whitney U-test.

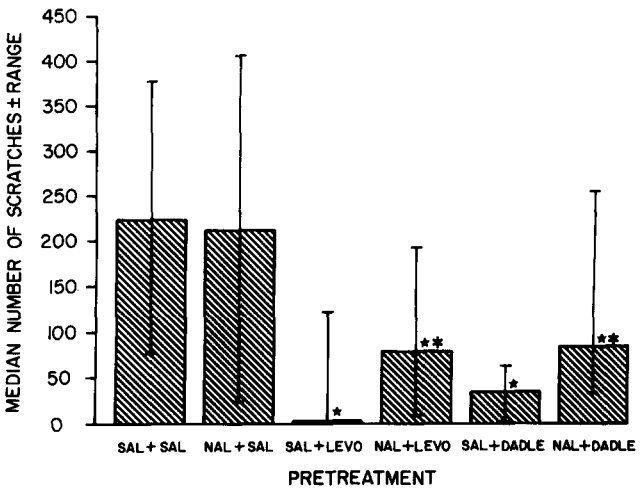

FIG. 3. Naltrexone antagonism of opioid inhibition of kainic acid-induced scratching. Rats were injected IP with either saline (SAL; 1 ml/kg) or naltrexone (NAL; 30 mg/kg) followed by 10 min by IT injection of either SAL (10 μl), levorphanol (LEVO; 90 nmol), or DADLE (10 nmol). Ten min later, kainic acid (0.5 nmol, IT) was injected and scratches were counted for 10 min. N = 17 for SAL+SAL, N = 10 for NAL+SAL, N = 11 for SAL+LEVO, and N = 6 for other gorups. $\star p<0.01$, compared to SAL+SAL, $*p<0.05$ compared to SAL+corresponding opioid using Mann-Whitney U-test.

phanol, which has a greater affinity than morphine to rat brain mu receptors (23), inhibited scratching both at 30 and 90 nmol. The highly potent and specific mu agonist DAGO (19,23) attenuated this behavior at 0.4 nmol and completely abolished scratching at 1.1 nmol. These findings strongly support participation of mu receptors in antagonism of kainic acid-induced scratching.

Although the mixed mu-delta agonist DADLE (7,23) diminished scratching at 10 nmol and completely blocked this behavior at 30 nmol, the highly selective delta agonist DPDPE (23,25) had no significant effect on this behavior at a higher dose (90 nmol), suggesting that delta receptors are not involved in opioid-induced scratch inhibition. Based upon the effectiveness of mu agonists, it would appear that DADLE inhibition of scratching is attributable to its activity at mu receptors.

Dextrorphan, the dextrorotary stereoisomer of levorphanol with activity at nonopioid PCP and sigma sites (8, 26, 28), significantly attenuated kainic acid-induced scratching, implying a role for PCP and/or sigma receptors. Further investigation confirmed this observation and indicated that scratching is also inhibited by PCP, a selective agonist at PCP sites (8,11), (+)-3-PPP, a sigma-specific ligand (8, 11, 12, 20–22), and (+)-NAM, the prototypical sigma agonist (24) which also interacts with PCP sites (8, 11, 21, 28). Based on these findings, it appears that both sigma and PCP sites mediate antagonism of kainic-induced scratching. Similarly, both receptors apparently mediate stereotyped behavior in rats (8).

Neither kappa agonist significantly altered scratching, arguing against a role for kappa receptors. Doses of dynorphin greater than 1.1 nmol could not be employed since hindlimb flaccidity and paralysis occurred, as previously reported (14). The nonsignificant reduction of scratching by EKC may be due to activation of mu and/or sigma receptors, since EKC has been shown to bind to these receptor subtypes (19, 22, 23, 29).

Based on the large dose employed (30 mg/kg), it was expected that naltrexone would completely antagonize both levorphanol- and DADLE-induced attenuation of scratching. The observed partial antagonism suggests that a non-mu mechanism may also be involved. Although neither DADLE (29) nor levorphanol (22) interacts with sigma sites, and binding of DADLE to PCP receptors has not been reported, it is known that levorphanol interacts with PCP sites (13, 26, 28). Further, naltrexone does not bind to PCP receptors (26,28) or antagonize the psychotomimetic effects of PCP (30). Thus, it is conceivable that the portion of levorphanol (and DADLE) activity that was not blocked by naltrexone is due to interaction of these opioids with PCP sites. Alternatively, the lack of complete antagonism by naltrexone could be attributable to partial activation of mu receptors, since high doses of naltrexone have been reported to elicit miosis in humans (31).

In recent studies using the mouse, both PCP (1,2) and opioids active at mu (2) or sigma (1,2) (but not delta or kappa) receptors antagonized scratching and biting caused by IT NMDA, but had relatively little effect on kainic acid-induced behaviors (2). These findings concur with present results insofar as the receptors mediating inhibition, but suggest a species difference in antagonism of kainic acid-induced behaviors. Perhaps in the rat kainic acid elicits its effects via the NMDA receptor; studies are underway to investigate this possibility and to determine if mu, sigma, and PCP agonists also inhibit behaviors induced by other excitatory amino acids.

In conclusion, the present study indicates that behaviors elicited by the excitatory compound kainic acid are subject to complex local circuit inhibitory controls. Opioids active at mu receptors inhibit scratching elicited by kainic acid, whereas selective delta or kappa agonists are without effect. Both opioids and nonopioids active at sigma and/or PCP sites also antagonize scratching. In addition, naltrexone pretreatment only partially antagonizes levorphanol- and DADLE-induced inhibition. Together, these results suggest that mu opioid, sigma and PCP receptors mediate inhibition of kainic acid-induced behavior. Considering the proconvulsive activity of this excitatory compound (9), it is not surprising that the circuitry activated by it is subject to multiple inhibitory regulatory influences.

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