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Morphine and Naloxone Act Similarly on Glutamate-Caused Guinea Pig Ileum Contraction

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KOYUNCUOĞLU, H., Y. ÜRESİN, Y. ESIN AND F. ARICIOĞLU. *Morphine and naloxone act similarly on glutamate-caused guinea pig ileum contraction.* PHARMACOL BIOCHEM BEHAV 43(2) 479–482, 1992. – Both morphine (M) and naloxone (NL) have been reported to have NMDA receptor blocking effects, regarded as the reason of opiate physical dependence development. On the other hand, glutamate (GLU) has been known to induce the contraction of isolated guinea pig ileum via acetylcholine release. Therefore, different concentrations of M or NL were investigated on the 1 mM GLU-induced contraction of isolated guinea pig ileum fixed at a resting tension of 1 g in isolated organ bath. The mean value (359.3 ± 20 mg) of the GLU-elicited contraction force was significantly reduced (318.4 ± 19.4) by 25 nM M concentration in the medium. Consequently, 500 and 750 nM M caused further decreases in a rather dose-dependent manner (270.8 ± 17.4 and 167.8 ± 16.5 mg, respectively). One micromolar M contraction nearly abolished (8.0 ± 8.2 mg) the GLU-induced contraction. A similar effect was obtained with the naloxone concentrations of 10, 20, 40, and 50 μM. In addition, NL has been shown to elicit the contraction of the isolated M-dependent guinea pig ileum. In the present study, 20- and 30-μM NL concentrations in the bathing medium caused the contraction of the ileum made M-dependent by preincubation with M (333.0 ± 32.4 and 309.5 ± 17.7 mg, respectively). These contraction forces were significantly reduced when the NL concentration was increased to 40 μM. And, 50 μM NL concentiation not only failed to induce contraction but caused a relaxation (−10.6 ± 2.3) as well. The results were considered supporting evidence for the fact that both M and NL are NMDA receptor blockers. While the affinity of NL for NMDA receptors is much higher than that of M, the blocking effect is much weaker than that of M. For this reason, NL precipitates abstinence syndrome in opiate-dependent mammals by displaying opiate from receptors without preventing them from having much stronger stimulation of aspartate and GLU than normal.

Morphine-like effect of naloxone NMDA receptor blockade Morphine Naloxone
Morphine-dependent guinea pig ileum Antagonism by morphine or naloxone of glutamate

SOME effects of intratechally administered excitatory amino acid (EAA) receptor agonists have been reported to be antagonized by opioids (1). Dynorphin (1–13), which interacts with the NMDA subtype of the EAA receptors (5), attenuates the intensity of opiate abstinence syndrome (9). Therefore, it has been assumed that opioids act as antagonists of NMDA receptors (14,19,20) and the upregulation and supersensitivity of the receptors due to this antagonism are the main reasons of the development of physical dependence upon opiates (14, 19,20). Although naloxone (NL) has almost generally been accepted as a "pure" opioid antagonist practically devoid of opioid-like agonistic action, it has already been reported to exert some opioid agonistic actions such as the induction of miosis in normal subjects (12,25), and analgesia in animals (33) and in man (22). When large doses of NL (150–300 mg), placebo, and morphine (M) (15–30 mg) were given to nondependent human volunteers, NL could not be identified clearly as an opioid agonist or antagonist (21). Moreover, the physiological and prolactin responses to NL closely resembled opioid agonist activity. As a matter of fact, it has been accepted that NL in this dose range behaves as an opiate agonist in man (21). In addition, a cross-tolerance between M and NL (13) and an increase by NL of the buprenorphine antinociception (4) were shown. Some experiments performed on the basis of the assumption and experimental results mentioned above have provided evidence supporting the fact that opioids including NL are NMDA receptor antagonists (15–18). For example, previous subchronic administration of M or NL intensified NL-induced abstinence syndrome in rats (15) just as did the noncompetitive NMDA antagonists ketamine and dextromethorphan (19). In this case, it has been pointed out that NL should possess a much higher affinity for NMDA receptors than addictive opioids while its NMDA receptor blocking effect seems weak (15). Similarly, administration of another

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noncompetitive NMDA receptor, antagonist MK801 (18), and an inhibitor of the release of the excitatory neurotransmitters aspartic and glutamic acids, tizanidine (17), caused an intensification of opiate physical dependence when administrations were carried out before or during the development of physical dependence. Furthermore, the combination of NL with ketamine, dextromethorphan, and M brought about a further intensification of the opiate physical dependence development, suggesting that NL, ketamine, dextromethorphan, and M act on the same receptors in the same direction (15). Finally, the attenuation of the opiate physical dependence development in young rats that had a partial destruction of NMDA receptors by mean of administration of monosodium glutamate during the neonatal period could support the blockade by opioids of NMDA receptors (16).

NL has been reported to induce a contracture in the isolated ileum taken from M-dependent guinea pigs (2,6). It has also been shown that the isolated guinea pig ileum taken from naive animals and exposed to opioids contracts after addiction of NL into the bathing medium (7,11,31,34). The contraction by NL of isolated ileum taken from M-dependent guinea pigs or naive animals then exposed to opioids is due to the release of acetylcholine (8,36). Consistent with this, the inhibition by M of the contracture of isolated guinea pig ileum and reduction by M of the acetylcholine output without any evidence to indicate the action of M on the cholinergic terminals have been reported (7,31). On the other hand, the existence of the NMDA receptors in the myenteric plexus of the guinea pig has long been known (28,29,37). In the Mg^{+2} free medium L-glutamic acid (GLU), L-aspartic acid (ASP), or D-GLU produce a rapid contraction of the isolated guinea pig ileum (37). The contraction can be antagonized by competitive and noncompetitive NMDA antagonists (37). This is quite consistent with the experimental findings indicating that stimulation of ASPergic/GLUergic receptors, especially NMDA subtypes, causes the release of acetylcholine (3,23,32,34,38), which is antagonized by opioids and noncompetitive NMDA receptor antagonists (3,38).

Taken together the information given above, it was thought of interest to investigate the effects of M and NL, which has been considered an opioid like M (15), on the GLU-elicited contraction in the isolated guinea pig ileum to provide further supporting evidence for the previous experimental findings regarding the blockade by opiates of NMDA receptors (14–16,19,20) and find out the probable mechanism underlying the inhibition by opiates of the gastrointestinal smooth muscle.

METHOD

Procedure

Guinea pigs fasting for 24 h were decapitated after cervical dislocation and terminal portions of their ilea were taken out. After they had been placed in Tyrode solution (NaCl 8.0 g, KCl 0.2 g, $CaCl_2$ 0.2g, $NaHCO_3$ 1.0 g, NaH_2PO_4 0.05 g, glucose 2.0 g, choline chloride 0.130 g) in a container, they were nicely and thoroughly washed by flushing Tyrode solution through the lumen. Consequently, they were cut into segments of 5 cm. Some of the segments were incubated in 1 μM M containing Tyrode solution at 4°C for 4 h (27,30). These segments were fixed at a resting tension of 1 g in 1 μM M containing Tyrode solution warmed at 37°C in an organ bath and washed out with the same Tyrode solution. The experiments with the other segments were carried out by using the same procedures without M. The Tyrode solutions were continuously bubbled with 95% O_2 and 5% CO_2.

At the end of the equilibration period, the sufficient quantity for 1 mM glutamate concentration from the previously prepared glutamate solution was added into the medium where the segments of ileum had been fixed. As soon as the maximum contractions of the isolated guinea pig ileum segment were seen, the necessary quantities of M or NL solutions were put into the medium to have 250-, 500-, 750-, and 1,000-nM (1 μM) M concentrations or 10-, 20-, 40-, and 50-μM NL concentrations, respectively. Into the M-containing Tyrode solution in which the ileum segments preincubated with M were suspended, sufficient quantities from the NL solution were added to provide 20-, 30-, 40-, and 50-μM NL concentrations in the medium. The contractions were recorded by means of a Nihon-Kohden SB-1T Force-Displacement Transducer, Nihon-Kohden RM-150 Polygraph (Tokyo, Japan), Acer 1120 SX PC, PC LAB PCL 718 A-D Converter (Taiwan, Taiwan), Labtech Acquire Data Acquisition Programme, and Lotus Data Analysis Program. Each segment was tested only once and every different M or NL application was repeated at least five times. The values of the contraction forces before the M or NL addition onto the contracted ileum by 1 mM GLU concentration were considered the control values and expressed as mg. All contraction forces or inhibition of the contractions were also expressed as mg in the tables.

All results were separately analyzed by one-way analysis of variance (ANOVA) and subsequently student's *t*-test was used for statistical evaluation.

Materials

Male inbred guinea pigs weighing 300–400 g fasting for 24 h were used. NL and M were purchased from Sigma Chemical Co. (St. Louis, MO) and Verenigde Pharmaceutische Fabrieken B.V. (Holland), respectively.

RESULTS

The mean values (±SD) of the inhibitory effect of the different M concentrations on the 1 mM GLU-induced contraction of the guinea pig ilea taken from naive animals and their statistical evaluations, after having been analyzed by one-way ANOVA and *t*-test, can be seen in Table 1. The

TABLE 1

MEAN VALUES OF THE INHIBITORY EFFECT OF DIFFERENT M CONCENTRATIONS IN THE BATHING SOLUTION ON THE CONTRACTION FORCE (mg) OF ISOLATED GUINEA PIG ILEA OBTAINED FROM NAIVE ANIMALS AND THEIR STATISTICAL EVALUATION BY *t*-TEST AFTER ONE-WAY ANOVA

Concentration	Contraction Force (mg)
1 mM GLU (20)	359.3 ± 20
1 mM GLU + 250 nM M (5)	318.4 ± 19.4*
1 mM GLU + 500 nM M (5)	270.8 ± 17.4*
1 mM GLU + 750 mM M (5)	167.8 ± 16.5*
1 mM GLU + 1,000 nM M (5)	8.0 ± 8.2*
F-value	368.380

The figures in parentheses indicate the number of experiments. GLU, glutamic acid; M, morphine.

*$p < 0.001$.

decrease in the 1-mM GLU-elicited contraction force of the ileum with the 250-nM M concentration was statistically significant ($p < 0.001$). The decrease in the contraction of the ileum was augmented with the increase of M concentrations to 500 or 750 nM ($p < 0.001$). This rather concentration-dependent inhibitory effect, which can be regarded as the antagonism of the contracting action of 1 mM GLU in the medium, reached the maximum point at 1,000 nM (1 μM) M concentration, showing probably a complete antagonism.

Table 2 shows the mean values ($\pm$SD) of the effects of the different NL concentrations provided after the 1-mM GLU-caused maximal contraction of the naive guinea pig ileum and their statistical evaluation. The 10-μM NL concentration appeared to significantly antagonize ($p < 0.01$). When concentration of NL added onto the contracted ileum was increased to 20 and 40 μM, the GLU-elicited contraction force significantly receded in a concentration-dependent manner from 395.4 to 262.6 and 122.8 mg, respectively ($p < 0.001$).

The mean values ($\pm$SD) of the contracting effect of the different NL concentrations in bathing solution on the guinea pig ileum made M dependent by preincubation with M and their statistical evaluation are shown in Table 3. The mean value of the contraction force induced by 20-μM NL concentration was 333 mg. When the NL concentration was increased to 30 μM, the mean value of the contraction forces decreased to 309.5 mg insignificantly. In the presence of 40 μM NL in the medium, the mean value of the contraction forces of the M-dependent ilea showed a statistically significant reduction in comparison with that seen with 20-μM NL concentration ($p < 0.001$). The increase of the NL concentration in the medium to 50 μM not only prevented the ilea from contracting but elicited even a relaxation whose mean value is -10.6 ($\pm$2.3) as well. The statistical comparison of the results obtained with the 50-μM NL concentration to those observed with the 20-μM NL concentration also showed a significant difference ($p < 0.001$).

DISCUSSION

In the present study, GLU induced a contraction of the guinea pig ileum obtained from naive animals (Tables 1 and 2) as previously shown. This GLU-induced contraction was antagonized by M in a rather concentration-dependent manner (Table 1).

TABLE 2

MEAN VALUES OF THE INHIBITORY EFFECT OF DIFFERENT NL CONCENTRATIONS IN THE BATHING SOLUTION ON THE CONTRACTION FORCE (mg) OF ISOLATED GUINEA PIG ILEA TAKEN FROM NAIVE ANIMALS AND THEIR STATISTICAL EVALUATION BY *t*-TEST AFTER ONE-WAY ANOVA

Concentration	Contraction Force (mg)
1 mM GLU (22)	359.4 ± 17.0*
1 mM GLU + 10 μM NL (6)	326.5 ± 18.0†
1 mM GLU + 20 μM NL (6)	262.6 ± 20.5†
1 mM GLU + 40 μM NL (5)	122.8 ± 12.2†
1 mM GLU + 50 μM NL (5)	21.2 ± 9.8†
F-value	433.954

The figures in parentheses indicate the number of experiments. GLU, glutamic acid; NL, naloxone.
*$p < 0.01$.
†$p < 0.001$.

TABLE 3

MEAN VALUES OF NL CONCENTRATION-ASSOCIATED REDUCTION IN THE NL-INDUCED CONTRACTION OF GUINEA PIG ILEA PREINCUBATED WITH AND MADE M DEPENDENT AND THEIR STATISTICAL EVALUATION BY *t*-TEST AFTER ONE-WAY ANOVA

NL Concentrations	Contraction Force (mg)
20 μM (6)	333.0 ± 32.4
30 μM (6)	309.5 ± 17.7
40 μM (5)	108.6 ± 19.5*
50 μM (5)	−10.6 ± 2.3*
F-value	293.64

The figures in parentheses indicate the number of experiments. NL, naloxone.
*$p < 0.001$.

The GLU-induced contraction of guinea pig ileum is not only antagonized by antimuscarinic compounds, tizanidine, noncompetitive NMDA receptor blockers, and the inhibitor of ASP/GLU release but by opioids as well (3,17,37,38). If the stimulation of NMDA receptors causes the release of acetylcholine (3,23,32,34,38), which induces the contraction of the guinea pig ileum, the antagonism by M in the present study, and by opioids and NMDA receptor antagonists in other studies (3,38), of the GLU-induced contraction of the guinea pig ileum can be related to the inhibition of acetylcholine release. In other words, opioids including M may block NMDA receptors as do other NMDA receptor blockers. This can surely be considered supporting evidence for the assumption concerning the blockade by opioids of NMDA receptors (14,19,20). On the other hand, NL also antagonized the GLU-elicited contraction of the guinea pig ileum at quite larger concentrations when compared to those of M (Table 2). Even though NL has almost unanimously been regarded as an opioid antagonist devoid of opioid-like actions, on the basis of some experimental results (4,12,13,21,22,25,33) supporting the fact that NL interacts with NMDA receptors (15–18) NL has been considered to have a quite high affinity for and weak blocking effect on NMDA receptors (15). When a small dose of NL is injected into an opiate-dependent mammal, it displaces the opiate and blocks NMDA receptors not sufficient to prevent the mammal from manifesting precipitated abstinence syndrome (15). The induction by NL of NMDA receptor upregulation also supports NL interaction with NMDA receptors as an antagonist (15). As a result, the use of the long-acting opioid antagonist naltrexone as a maintenance treatment following opiate detoxification (35) can be easily explained with the identical action of NL to that of M on NMDA receptors. Furthermore, the reason underlying the complete suppression by continuous NL administration of withdrawal signs after the acute blocking by the short-acting barbiturate methohexitone of NL-precipitated opiate withdrawal in opiate-addicted persons (26), the attenuation by NL of abstinence-exacerbated grooming, body-shaking, teeth-chattering, and sneezing, and the complete antagonism by NL of withdrawal hyperalgesia in postdependent animals (10) and finally the very short transition from methadone to naltrexone maintenance of opiate-addicted patients after NL administration under the sedative effect of the fully reversible short-acting benzodiazepine derivate midazolam (24) would result

from the NMDA receptor blocking effect of NL. The experimental results shown in Table 3 can be considered compelling evidence for the above explanations. While the lower concentration of NL in the medium can cause the contraction of the guinea pig ileum made M dependent by means of preincubation with M, the higher concentrations appear to lessen the contractions and at a certain concentration the contraction-inducing effect of NL becomes even a relaxing effect (Table 3) due to a complete blockade of NMDA receptors whose stimulation causes acetylcholine release.

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