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Previous Chronic Blockade of NMDA Receptors Intensifies Morphine Dependence in Rats

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KOYUNCUOĞLU, H. AND F. ARICIOĞLU. *Previous chronic blockade of NMDA receptors intensifies morphine dependence in rats.* PHARMACOL BIOCHEM BEHAV **39**(3) 575–579, 1991.—Chronic exposure of receptors to antagonists generally results in upregulation and/or supersensitivity. On the other hand, the noncompetitive NMDA receptor antagonists ketamine (K) and dextromethorphan (DM) suppress opiate abstinence syndrome by blocking NMDA receptors. Therefore, 40 mg/kg ketamine (K), 5 mg/kg dextromethorphan (DM), 5 mg/kg morphine (M) and 2 mg/kg naloxone (NL) alone or in combination with NL were IP administered to the rats five times during the daytime only for five days to see whether they would intensify abstinence syndrome through upregulation and/or supersensitivity of NMDA receptors. Three days following the implantation of three M-containing pellets, abstinence syndrome was brought about by 2 mg/kg NL injection. Jumping, wet dog shake, writhing, teeth chattering, diarrhoea, defecation and ptosis were observed for ten min. All drugs used alone or in combination with NL increased the intensity of abstinence syndrome. Since K and DM are noncompetitive NMDA receptor antagonists, the intensifying effect of NL or M was considered to be related to their interactions with NMDA receptors. Furthermore, on the basis of the results of the previous and present study, NL was claimed to act on NMDA receptors, like other opioids, but with higher affinity for and weaker blocking effect on NMDA receptors.

Ketamine Naloxone Morphine Dextromethorphan Previous blockade of NMDA receptors Intensification of abstinence syndrome

CHRONIC receptor antagonist treatment generally results in a compensatory increase in the number of functional receptors called upregulation. The increase in the sensitivity of the receptors to their agonist is known as supersensitivity. The supersensitivity of opioid binding sites developed by opioid antagonists such as naloxone (NL) and naltrexone (NX) has been reported under various conditions, and the exposure to the antagonist of the binding sites renders previously ineffective doses effective. Both supersensitivity and upregulation are believed to subside within days of the discontinuation of exposure to antagonist (24, 28, 29, 35, 36, 40). On the other hand, the development of the supersensitivity at the opioid binding sites has been reported during a regimen of morphine (M) and NX injections. As a result, the influencing effect of agonist on the development of supersensitivity should be taken into consideration (39).

Ketamine (K) and dextromethorphan (DM), having no addiction liability (17, 19, 27), have been reported to possess an attenuating effect on the responses to the stimulation of the aspartatergic (ASPergic)/glutamatergic (GLUergic) receptor subtypes, especially N-methyl-D-aspartate (NMDA) (2, 3, 8, 12, 13). The attenuating effect of K and DM on the actions of NMDA is related to their noncompetitive blockade of the ion channel associated with the NMDA receptor (2, 11, 13, 30). These properties of K and DM were successfully used to suppress the precipitated abstinence syndrome in rats (21), because the mechanisms underlying the physical dependence on opiates have been experimentally shown to be the inhibition by opiates of the enzymes which produce the neurotransmitters ASP and GLU from asparagine and glutamine, and the blockade and subsequently the upregulation and supersensitivity of the ASPergic/GLUergic receptors (21). Consequently, DM has successfully been used in the treatment of opiate-addicted persons (22).

In light of the experimental results mentioned above, it would be of interest to investigate the effects of the subchronic blockade by the noncompetitive NMDA receptor antagonists K and DM of the NMDA receptors on the precipitated abstinence syndrome in rats which would be rendered M dependent just after the discontinuation of the K and DM administration. Additionally, the administration of M and NL before the development of physical dependence on M could give further information in connection to their relationship with the blockade of NMDA receptors in the mechanisms of the opiate dependence development and the intensity of the precipitated abstinence syndrome, since the opioid mu, delta and to a lesser extent, sigma receptor agonists have been shown to antagonize some effect of intrathecally (IT) administered excitatory amino acid agonists (1), K and DM suppress the abstinence syndrome signs in rats (21), as well as in man (22). Finally, dynorphin (1–13) which interacts with NMDA receptors (7), attenuates the intensity of opiate withdrawal symptoms (14).

METHOD

The rats were divided into nine groups. The first group (Control) was intraperitoneally (IP) injected with physiological saline at 0900, 1100, 1300, 1500 and 1700. The third, fourth, fifth and sixth groups were IP administered 40 mg/kg K, 2

TABLE 1

THE MEAN VALUES (±SE) OF THE ABSTINENCE SYNDROME SIGNS AND THEIR STATISTICAL EVALUATIONS

Groups	Jumping	Wet Dog Shake	Writhing	Teeth Chattering	Diarrhoea	Defecation	Ptosis	Total Evaluation of the Signs
Control (10)	3.20 ±0.25	1.30 ±0.21	0.30 ±0.30	8.60 ±0.34	0.30 ±0.21	7.10 ±0.28	1.00 ±0.30	89.9
I. K (11)	5.27** ±0.67	2.45** ±0.36	0.09 ±0.09	7.63 ±0.61	0.45 ±0.16	8.90* ±0.70	1.27 ±0.33	108.22
II. K (12)	7.91*** ±0.58^{aa}	4.91*** ±0.31^{aaa}	1.17 ±0.67	4.17*** ±0.96	0.92* ±0.19	9.84** ±0.91	0.92 ±0.38	137.27
NL (10)	6.30*** ±0.45	3.90*** ±0.23	0.00 ±	8.20 ±0.70	0.60 ±0.16	5.30** ±0.36	1.60 ±0.27	123.1
M (10)	7.80*** ±0.49	4.40*** ±0.34	0.10 ±0.09	6.60*** ±0.30	0.30 ±0.15	5.70*** ±0.40	1.70* ±0.15	127.8
DM (12)	9.84*** ±0.98	3.84*** ±0.55	0.25 ±0.18	8.33 ±0.69	1.08* ±0.26	7.67 ±0.78	2.17** ±0.21	163.21
N+I. K (12)	9.75*** ±1.37^{bbb}	4.08*** ±0.57^{bbb}	0.50 ±0.23^{bbb}	5.34*** ±0.77^{bbb}	0.67 ±0.25^{bb}	9.66** ±0.94^{b}	1.25 ±0.28	146.13
N+M (9)	14.55*** ±1.82$^{ccc\text{-}dd}$	3.88** ±0.69	0.00 ±	3.56*** ±1.07$^{cc\text{-}dd}$	1.23** ±0.28^{dd}	9.22** ±0.72$^{ccc\text{-}ddd}$	1.78 ±0.4	169.5
N+DM (11)	10.18*** ±1.07^{ee}	4.90*** ±0.69	0.00 ±	5.54** ±0.78$^{ee\text{-}gg}$	1.81** ±0.23$^{eee\text{-}g}$	8.90** ±0.51^{eee}	2.09** ±0.16	162.01

The figures in parentheses indicate the numbers of rats in the groups.

* → <0.05, ** → <0.02, *** → <0.001 The statistical significance referring to control values.

aa → <0.02, aaa → <0.001 The statistical significance between I. Ketamine and II. Ketamine groups.

b → <0.05, bb → <0.02, bbb → <0.001 The statistical significance between I. Ketamine and Naloxone + I. Ketamine groups.

cc → <0.02, ccc → <0.001 The statistical significance between Naloxone and Naloxone + Morphine groups.

dd → <0.02, ddd → <0.001 The statistical significance between Morphine and Naloxone + Morphine groups.

ee → <0.02, eee → <0.001 The statistical significance between Naloxone and Naloxone + Dextromethorphan groups.

g → <0.05, gg → <0.02 The statistical significance between Dextromethorphan and Naloxone + Dextromethorphan groups. I. Ketamin → I. K., II. Ketamine → II. K, Naloxone → NL, Dextromethorphan → DM, Naloxone+I. Ketamine → NL+I. K, Naloxone+Morphine → NL+M, Naloxone+Dextromethorphan → NL+NL+DM.

mg/kg NL, 5 mg/kg M and 5 mg/kg DM in the same volume of physiological saline also at 0900, 1100, 1300, 1500 and 1700. They were called I. Ketamine, Naloxone, Morphine and Dextromethorphan group, respectively. The second group (II. Ketamine) received 40 mg/kg IP seven times a day with equal intervals. The seventh, eighth and ninth groups were IP administered 40 mg/kg K, 5 mg/kg M and 5 mg/kg DM in a similar manner to I. Ketamine, Morphine and Dextromethorphan, but all the rats belonging to the latter groups were given 2 mg/kg NL IP ten min before the IP administration of K, M and DM. These groups were later mentioned as Naloxone + I. Ketamine, Naloxone + Morphine and Naloxone + Dextromethorphan groups. The administration of the drugs as given above lasted five days. On the fifth day, one hour after the last injection, three pellets containing 75 mg M base (total 225 mg) (37) were subcutaneously implanted on the back of all the rats under light ether anesthesia.

Three days following pellet implantation, all the rats were IP injected with 2 mg/kg NL and they were immediately placed in a metal cage (base area: 20×22 cm, height 20 cm). Then the number of jumps, wet dog shakes, writhing, teeth chatterings and defecations were counted for ten min. Diarrhoea and ptosis were rated 1, 2 or 3, whereas teeth chattering was rated 1, 2, 3, . . . 10 according to the severity. Additionally, on the basis of Himmelsbach's Degree Method (16) which characterizes the abstinence syndrome into four grades to reflect the clinical severity, and the correlations among the occurrence, onset and fading of each abstinence syndrome signs in accordance with the M content of the implanted pellet(s), the exposure time of the animals to different M content pellet(s) and the amount of NL used for precipitated abstinence syndrome (5), each sign was rated as follows. Every jump, wet dog shake, writhing, maximum degree of teeth chattering, diarrhoea, defecation and ptosis was separately scored 8, 4, 10, 5, 10, 1 and 3, respectively. The total score of each category was shown as a total evaluation of the abstinence syndrome severity in the last column of Table 1 in order to give overall information of the seven signs for each group.

Materials

Male Wistar inbred rats (weighing 140–180 g) kept in a room 22–23°C on a 12-hour light/dark cycle and fed with a standard regimen ad lib were used. DM was a gift from Roche (Basel, Switzerland). NL, M and K were purchased from Sigma (St. Louis, MO), Sandoz (Basel, Switzerland) and Padeko (Istanbul, Turkey), respectively.

RESULTS

The mean values (±SE) of the abstinence syndrome signs counted or rated in each group and their statistical evaluation among them are shown in Table 1. In addition, the total evaluation of the signs obtained from the sum of the scores, which was given to every single sign on the basis of their significance in determining the severity of the abstinence syndrome in each category, can also be seen in the last column of Table 1.

The rats belonging to I. K and II. K groups showed a stronger abstinence syndrome than control. On the other hand, the intensity of the abstinence syndrome in the rats of II. K is clearly

more pronounced than in those of I. K group.

The intensity of the syndrome manifested by the rats of NL and M groups is also higher than control. But no statistically significant difference was found between the two groups, at least at the doses applied before the development of the M physical dependence.

The highest intensification of the physical dependence was seen in the rats injected with DM before the development of M physical dependence.

The combination of K, M and DM with NL administration ten min before K, M and DM injections caused further intensification of the M physical dependence observed in the rats of NL group.

DISCUSSION

Before starting to discuss the results of the present study, the point with respect especially to teeth chattering, which seems to be inconsistent with an increase or decrease of the other abstinence syndrome signs, should be clarified. Among the signs, those such as flying, jumping and diarrhoea are considered "dominant," while some others, such as wet dog shake and teeth chattering, are classified "recessive." When the intensity of "dominant" ones increases, the intensity of some, if not all, "recessive" ones generally decreases and vice versa (5).

On the basis of the present experimental results, it can be said that the subchronic administration of K, N, M, and DM, regardless of their binding sites at the NMDA receptor including its associated components, invigorated the intensity of the precipitated abstinence syndrome. Two of four administrated drugs, namely K and DM, have been reported to be noncompetitive NMDA receptor antagonists (2, 3, 8, 10, 12, 13, 29) and to suppress opiate abstinence syndrome in rats (21) and in men (22). As a result, the intensifying effect of K and DM administered before the development of opiate physical dependence on the opiate precipitated abstinence syndrome appears to be consistent with the fact that subchronic exposure of the receptors to one of their antagonists causes the upregulation and/or supersensitivity of the NMDA receptors, if the hypothesis related to the mechanisms underlying the opiate physical dependence (21,22) works. In other words, the previous blockade by K and DM of the consequences of the activated NMDA receptors leads to an increase in the number and/or sensitivity of the NMDA receptors. After M-containing pellet implantation, the number and/or sensitivity of the NMDA receptors has a further increase due to yet another large blockade by M as a result of the assumption regarding the mentioned mechanisms (21,22) which lately appeared to have been almost proven in rats (21) and in men (22) experimentally. Following NL injection which must remove M from the site(s), where M bound, brings about abrupt withdrawal. Consequently, the NMDA receptor whose number and/or sensitivity had excessively been augmented is much more stimulated by ASP and GLU, probably more pronounced than normal (21,22). Due to these events, a much more intense abstinence syndrome is manifested by the rats previously given K or DM than by those not given K or DM previously. This explanation would be acceptable at least for K and DM which have long been known as noncompetitive NMDA receptor antagonists (2, 3, 8, 10, 12, 13, 29). Even though the doses of K and DM used in the experiments might have been found higher and lower, respectively, than the doses reversing NMDA-induced seizures and producing an anticonvulsant effect in a maximal electroshock (MES) test, they appeared to be more or less optimum to reach the aims of the present study. A rather shorter-lasting effect and lower doses can be enough to reverse NMDA-induced seizures and to produce anticonvulsant action in a MES test, especially when K is administered intravenously. The reasons for the administration of K at relatively high doses are that the administration was carried out intraperitoneally, which increases the first passage through the liver and the relatively high doses could have augmented the blocking time of NMDA receptors as long as possible to cause upregulation and/or supersensitivity. In fact, the intensity of the abstinence syndrome in II. K group, which had seven IP injections of 40 mg/kg a day, is stronger than in the I. K group which received only five IP injections of 40 mg/kg a day (Table 1). The dose of DM used in the present study was chosen after having had a suppressive effect with 3 mg/kg on the precipitated abstinence syndrome in rats (21). As a result, since the opiate abstinence syndrome is not comparable with NMDA-induced seizures and MES test, the dose of DM was decided to be 5 mg/kg. Furthermore, the 5 mg/kg dose of DM could have given some more comparative information about the site of the blockade and the possibility of making some quantitative comparisons among NMDA blocking drugs. Additionally, as seen in Table 1, 5 mg/kg DM caused a relatively higher intensification of the abstinence syndrome, indicating that higher doses would not have been needed.

With regard to the intensifying effect of NL and M, additional information is needed. Both K and M induce a dose-related analgesia; they also cause catatonia, then catalepsy at larger doses. Both K- and M-induced analgesia and catatonia are NL reversible (15,38). As is known, K interacts with opioid receptor binding sites (18, 32, 33). As a consequence, it has been assumed that interactions with K receptors could modulate pain pathways in a manner similar to those opioids (34). As the pharmacological effects of K and M are similar, the interactions between various subeffective dose combinations of K and M were investigated, and it has been shown that the combination of individually subeffective doses of K and M induced catalepsy (15). In addition, a complex relationship between K and M administered concomitantly, in connection with behaviour, potentiation, tolerance, cross-tolerance and antagonism by NL were found (15). These experimental results were further supported by using synthetic opioids (4). Moreover, it has recently been demonstrated that opioids, phencylidine and sigma agonists antagonize excitatory amino acid-induced nociceptive action and other behavioural changes (1). On the other hand, opioids do not antagonize only NMDA receptor agonist-induced behaviours, but IT administered kainic acid-induced behaviours as well (20). In this study, the IT pretreatment of the selective mu agonist levorphanol, [D-Ala^2, N-Met-Phe^4, Gly^5-Ol]-enkephalin (DAGO), or M, the mixed mu-delta agonist [D-Ala^2, D-Leu^5]-enkephalinamide (DADLE), or the sigma/phencyclidine agonist dextrorphan or (+)-N-allyl-N-normetazocine inhibited the effects of IT-administered kainic acid. Levorphanol- and DADLE-induced behaviours were partially antagonized by naltrexone (NX) (20). Additionally, the benzomorphan derivatives cyclazocine and pentazocine have been shown to selectively reduce neuronal excitations evoked by N-methylaspartate (10); NX was found to reduce the NMDA neurotoxicity in vitro (9); large doses of NL (150–300 mg) were shown to act as an opiate agonist in men (23). On the other hand, if M binds and blocks NMDA receptors in the development of opiate physical dependence as assumed (21,22), the abstinence-precipitating effect of NL can be supporting evidence that NL interacts with NMDA receptors. Finally, if 2 mg/kg NL injected five times only during the daytime for five days causes an intensification of the abstinence syndrome more or less equal to the intensification of 5 mg/kg M administered similarly, it would be logical to say that NL binds and blocks NMDA receptors. As seen in Table 1, the administration of 2 mg/kg NL ten min before a 5 mg/kg administration of M, whose analgesic and blocking effects are not antagonized

by NL given ten min before due to the badly undisturbed and unaltered occupation by M of NMDA receptors modulating pain transmission and perception, shows an additive effect on the effect of M. This might be compelling evidence that NL and M act in the same direction at the same place at least in the development of physical dependence and the opiate abstinence syndrome. The difference between their doses in the intensification, in the precipitating abstinence syndrome and even in the antagonism by NL of the M analgesia, clearly indicates that the affinity of NL for NMDA receptors is higher than that of M. All the information given above implies that NL and M interact with the ASPergic/GLUergic receptors. According to our recent experimental studies performed by using a new NMDA receptor antagonist SDZ EAA 494 (CPP ene, Sandoz, Basel, Switzerland), SDZ EAA 494 has an abstinence syndrome precipitating effect in the rats rendered M dependent by M-containing pellet implantation technique and NL-reversible antinociceptive effect. The abstinence syndrome precipitating effect of SDZ EAA 494 intensifies that of NL when SDZ EAA 494 is administered five min before NL. The antagonism by NL of SDZ EAA 494-induced antinociception turns into a synergism at higher doses; the antinociceptive effect of SDZ EAA 494 increases more than expected. Additionally, 8 mg/kg NL alone causes analgesia itself (manuscript in preparation). Although NL has long been accepted as a "pure" opioid antagonist, practically devoid of opioid like agonistic actions, it has been shown that NL exerts some analgesic effects in man (25). Moreover, NL induces miosis in normal subjects (18,26) and a NL analogue NX has slight opioid agonist activity (6).

In light of the information given above, one can have the impression that NL is a NMDA receptor antagonist just like M and other opioids in a general sense. It should possess higher affinity for NMDA receptors and less preventing effect on NMDA receptors from ASP and GLU, because NL removes other opioids from the receptors, but it cannot prevent the receptors from the stimulating effects of their endogenous transmitters which result in the manifestation of abstinence syndrome (21,22). This may be why previously administered NL intensifies opiate physical dependence and the administration of NX is helpful in preventing relapses in postopiate addicts (31).

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