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# Influences of Electrolytes on the Action of Morphine and Naloxone in Guinea-pig Ileum

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=국문초록=

## 海獐 回腸片에서 Morphine과 Naloxone作用에 미치는 電解質의 影響

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Guinea-pig의 myenteric plexus-longitudinal muscle preparation에서 morphine과 naloxone 效果에 미치는 電解質의 影響을 觀察하였다. 標本은 Krebs-Henseleit bicarbonate buffer solution으로 채운 organ bath에 懸垂하고 0.2Hz로 電氣刺戟하였다.

Morphine은 電氣刺戟에 依한 筋片收縮을 抑制하였으며, 이때 $ID_{30}$은 約 190nM이었다. 이와같은 morphine의 抑制作用은 bath內 $Na^+$ 또는 $K^+$ 濃度를 減少시키거나 $Mn^{2+}$을 加하면 强化되었으며, $Ca^{2+}$ 濃度를 增加시키거나 $Mg^{2+}$ 濃度를 減少시키면 弱化되었다.

Naloxone은 morphine의 作用을 抑制하였으며, 이때 naloxone에 對한 affinity index인 $pA_2$ value는 約 8.8이었고 bath內 電解質 濃度를 變動시켜도 影響받지 않았다.

이 成積은 電解質 變動으로 因한 morphine의 作用變動은 電解質이 opiate receptor의 affinity를 變動시킨다는 opiate-receptor binding實驗에서와는 달리 電解質 變動에 依한 functional opiate receptor의 affinity 變動에 依한 것이 아님을 示唆한다.

=Abstract=

The influence of electrolyte concentrations on the action of morphine and naloxone was studied in the myenteric plexus-longitudinal muscle preparation of guinea-pig ileum to examine whether opiate receptor binding obseved *in vitro* with homogenates represents binding to the pharmacological receptor. The preparations were suspended in a modified Krebs-Henseleit bicarbonate buffer solution and electrically stimulated at 0.2 Hz. Morphine inhibited electrically evoked contractions; the concentration of morphine required for a 50-percent inhibition was 190 nM. This inhibitory action of morphine was potentiated in a medium containing lower concentrations of $Na^+$ or $K^+$, or by the addition of $Mn^{2+}$ to the medium, and weakened by increasing the concentration of $Ca^{2+}$ or decreasing the concentration of $Mg^{2+}$. Naloxone antagonized these

actions of morphine; however, $pA_2$values for naloxone (indices of affinity for antagonists, approximately 8.8) were unaffected by these electrolyte concentrations. Thus, changes in the inhibitory action of morphine caused by alterations in electrolyte concentrations are probably not the result of changes in the affinity of the receptor for opiates, but due to alterations in the events which precede or follow the receptor binding. Effects of electrolytes on the affinity of the functional opiate receptor for naloxone in guinea-pig ileum are apparently different from those reported with the specific binding sites for opiates in brain homogenates.

## INTRODUCTION

The saturable binding of opiate agonists and antagonists observed *in vitro* is proposed to represent the binding of opiates to their pharmacological receptors (Pert and Snyder, 1973a, 1974; Terenius, 1974; Kosterlitz and Waterfield, 1975). This is primarily based on the finding that a good correlation can be observed between the affinities of binding sites for opiate agonists and antagonists and their pharmacological potencies, and that the distribution of the saturable binding sites is limited to the neuronal tissue at which the pharmacological actions of opiates can be demonstated. It is not firmly established, however, that the binding of labelled opiate agonists and antagonists observed *in vitro* actually represents the binding of these agents to the pharmacological receptors.

Saturable opiate binding has been shown to be sensitive to treatments which the integrity of the cytoplasmic membrane and to changes in electrolyte concentration in the incubation medium (Simon *et al.*, 1973; Pasternak and Snyder, 1974, 1975; Hitzemann *et al.*, 1974; Davis *et al.*, 1977, 1978, 1979). In an earlier report, pert *et al.* (1973) demonstrated that sodiumion decreases opiate agonist binding and increases opiate antagonist binding. These investigators suggested that the observed effects of sodium are the result of sodium-induced alterations in receptor conformation which decreases agonist binding sites and increases antagonist binding sites. In contrast, Simon *et al.* (1973) reported that the sodium-induced increase in antagonist binding is primarily due to an increased affinity and is not the result of the unmasking of new binding sites. This discrepancy is further complicated by the presence of two types of naloxone binding sites in the brain tissue (Lee *et al.*, 1975). It is generally accepted, however, that sodium decreases agonist binding and increases antagonist binding, whereas potassium decreases both agonist and antagonist binding.

It has also been shown that the saturable binding of agonists is enhanced by divalent cations such as $Mn^{2+}$, $Mg^{2+}$, $Ni^{2+}$ and$Ca^{2+}$, whereas that of antagonists is either unchanged or inhibited (Pasternak *et al.*, 1975). These effects of electrolytes on the opiate receptor provide us with an opportunity to examine whether the binding of opiates observed *in vitro* is related to their binding to pharmacological receptors. Such studies, however, are difficult with brain tissue, since their functions cannot be readily monitored under conditions in which electrolyte concentrations are altered.

The present studies were carried out with the myenteric plexus-longitudinal muscle preparation of guinea-pig ileum, since this pre-

paration has been successfully used by several investigators to study the actions of opiate agonists and antagonists (Paton, 1957; Cox and Weinstock, 1966; Gyang and Kosterlitz, 1966; Kosterlitz and Watt, 1968; Fennessy *et al.*, 1969; Kosterlitz *et al.*, 1973). The presenece of saturable opiate binding sites in these preparations has also been demonstrated (Pert and Snyder, 1973b; Creese and Snyder, 1975). Using these preparations, the effects of electrolytes on the action of morphine and naloxone were studied and compared with the known effects of electrolytes on opiate receptor binding.

## MATERIALS AND METHODS

Guinea pigs of either sex weighing 350 to 450 g were stunned by a blow to the head and the small intestine was immediately remosed. The ileum was cut 10 cm above the ileocecal junction and placed in a modified Krebs-Henseleit solution of the following composition: 118 mM NaCl, 27.2 mM $NaHCO_3$, 4.8 mM KCl, 1.0 mM $KH_2PO_4$, 1.2 mM $MgSO_4$, 1.8 mM $CaCl_2$ and 11.1 mM glucose. Subsequently, a 4-cm muscle strip of ileum was excised, cut along the longitudinal axis, and suspended between two parallel platinum electrodes placed 1 cm apart in the above solution saturated with a 95% $O_2$-5% $CO_2$ gas mixture at 37°C (pH 7.4). Field electrical stimulation (0.2 Hz, 10 ms duration and 50 V/cm) was applied and the force of isometric contraction was recorded by using a force-displacement transducer (Grass Instrument Co., Quincy, M; model FT−03C) and a model 2400 Brush recorder (Gould Inc., Cleveland, OH). Resting tension was adjusted to approximately 0.5 g. After a 60-min equilibration, morphine was added to the incubation medium, and its effect on force of contraction was observed until a steady state was reached. Subsequently, morphine was washed five times with a drug-free solution, and another concentration of morphine was added to the incubation medium after a steady control state was established.

To study the affinity of the functional binding sites for naloxone, the effects of morphine were examined in the presence of various concentrations of naloxone, and $pA_2$ values were obtained using the method described by Arunlakshana and Schild (1959). The concentration of morphine required to cause a 50-percent inhibition of the evoked contraction was estimated from the linear regression line fitted to the plots of log [Y/(1-Y)] aga-

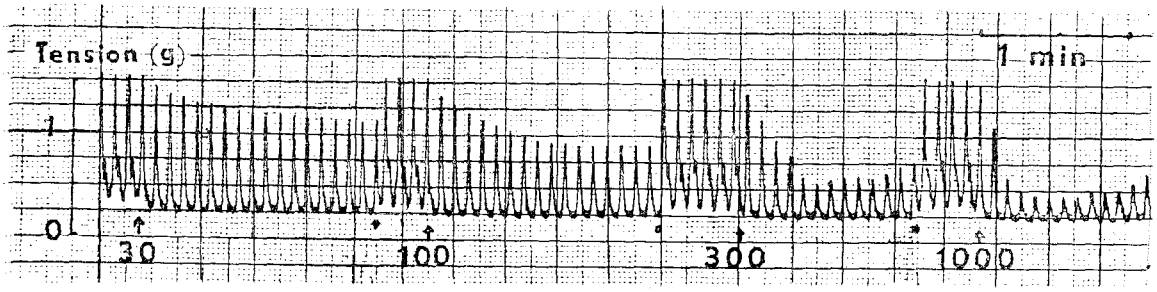


**Fig. 1.** Effects of morphine on the force of contraction in isolated guinea-pig ileum. Preparations were electrically stimulated at 0.2 Hz at 37°C. At the time indicated by the arrow, morphine sulfate (final concentraction in nM) was added to the medium. At the time indicated by the dot, the recording was stopped, and medium was changed five times with a drug-free solution.

inst the morphine concentration on a logarithmic scale by the least square method, where Y is the fractional activity observed in the presence of morphine (Goldstein *et al.*, 1974). The value of $pA_2$ was estimated by fitting a linear regression line to the plots of log (DR−1) against the logarithmic concentration of naloxone by the least square method, where DR is the dose ratio of morphine in the presence and absence of naloxone.

Morphine sulfate was obtained from Mallinckrodt Chemical Works, St. Louis, MO, and naloxone hydrochloride from Endo Laboratories, Brussels, Belgium. These drugs were dissolved in a modified Kreds-Henseleit bicarbonate buffer solution. All other chemicals were of reagent grade.

## RUSULTS

### 1) Effects of morphine on the force of contracion

After a 60-min equilibration period, the evoked contraction and resting tension of the isolated guinea-pig ileum were stable for at least 8 hours. The addition of morphine sulfate to the incubation medium caused a concentration-dependent inhibition of force of contraction which reached a steady stase within one min (Fig. 1). A complete inhibition of the electrically evoked contraction was observed with higher concentrations of morphine. Resting tension was also sl.ghtly decreased. When the drug was thoroughly washed out, both developed and resting tension returned to the control value. Repeated administrations of morphine at 20-min intervals produced a reproducible inhibition of contraction indicating that a complete concentration-response curve may be obtained with each preparation. The

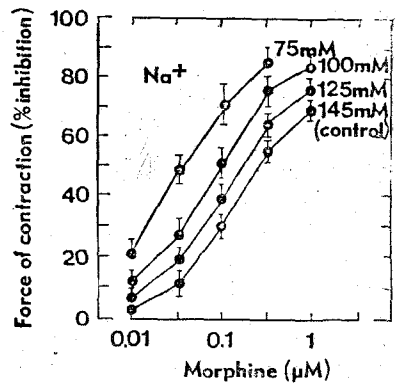


Fig. 2. The effect of $Na^+$ on the inhibitory action of morphine. Preparations were electrically stimulated at 0.2 Hz in a modified Krebs-Henseleit bicarbonate buffer solution in which $Na^+$ concentration was altered using sucrose as an osmotic substitute. After equilibration, the inhibitory action of morphine was studied as shown in Fig. 1. Developed and resting tension observed in a medium containing 145 mM $Na^+$ (controls) were 1.09±0.05 and 0.47±0.02 g, respectively (mean±S.E. of 8 preparations). See text for changes in developed tension caused by alterations in $Na^+$ concentration. Each point represents the mean of 8 experiments. Vertical lines indicate S.E.

concentration-response curve for morphine obtained with this method was slightly different from that obtained with cumulative additions of morphine to the incubation medium (data not shown). Therefore, morphine was washed out after the effect of each morphine concentration was observed in the following experiments.

### 2) Effects of monovalent ant divalent cations on the action of morphine

Since both $Na^+$ and $K^+$ have been shown to inhibit the saturable binding of opiate agonists to brain homogenates (Simon *et al.*, 1973; Pert and Snyder, 1974) but perhaps by different mechanisms (Akera *et al.*, 1975; Lee *et al.*, 1977), the effects of these cations on the

action of morphine were examined first. The control concentration-response curve for the inhibitory action of morphine on force of elcctrically evoked contraction was estimated in each preparation. Subsepuently, the incubation medium was changed to that containing either a reduced $Na^+$ or $K^+$ concentration adjusting the osmolarity with sucrose, and the concentration-response curve for morphine was obtained again.

When the resting tension was set at 0.5 g and the preparation was stimulated at 0.2 Hz, average developed tension was 1.90±0.05 g (mean ± S.E. of 10 preparations) in a medium containing 145 mM $Na^+$ and 5.8 mM $K^+$. A reduction in $Na^+$ conceotration caused a slight decrease in developed tension. The developed tensionse observed in low $Na^+$ media in the absence of morphine were 8.9±2.8% (125 mM $Na^+$), 15.±4.4% (100 mM $Na^+$) and 23.8±2.8% (75 mM $Na^+$) lower than the above control value. High concentrations of morphine were again capable of causing a complete inhibition of contration in the medum containing the reduced $Na^+$. When the concentration of $Na^+$ was decreased, the inhibitory action of morphine was significantly increased as indicated by a parallel shift in the concentration-response curve for morphine to the left (Fig. 2). The extent of the shift was almost ten-fold; the concentration of morphine needed to cause a 50% inhibition of force of contraction in the presence of 145 mM $Na^+$ and 5.8 mM $K^+$ was 190 nM, whereas the corresponding value observed in a medium containing 75 mM $Na^+$ and 5.8 mM $K^+$ was 21 nM.

A reductin in $K^+$ concentration also decreased the developed tension. In the medium containing 145 mM $Na^+$ and 2.9 or 1.45 mM $K^+$, the developen tension was 15.2±2.9 % and 29.5±3.3%, respectively, lower than control

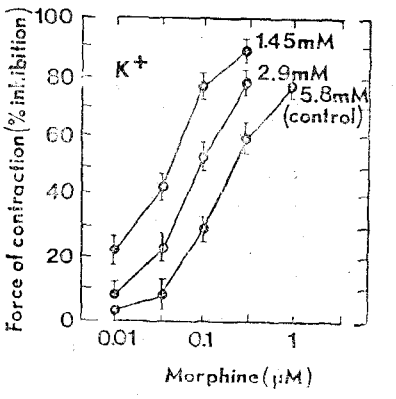


Fig. 3. The effect of $K^+$ on the inhibitory action of morphine. See legend to Fig. 2. The concentration of $Na^+$ was fixed at 145 mM, and the concentration of $K^+$ in the medium was changed as indicated. Each point represents the mean of 8 experiments.

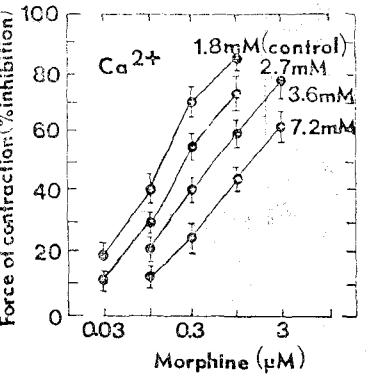


Fig. 4. The effect of $Ca^{2+}$ on the inhibitory action of morphine. See legend to Fig. 2. The concentraction of $Na^+$ was fixed at 145 mM, and the concentration of $Ca^{2+}$ in the medium was changed as indicated. Each point represents the mean of 6 experiments.

values observed in the presence of 5.8 mM $K^+$. The decrease in $K^+$ also enhanced the inhibitory action of morphine (Fig. 3). Again, a parallel shift to the left in the concentration-Inhibition curve for morphine was observed. The concentration of morphine needed to cause a 50% inhibition of developed tension in the presence of 1.45 mM $K^+$ was 25 nM. Thus,

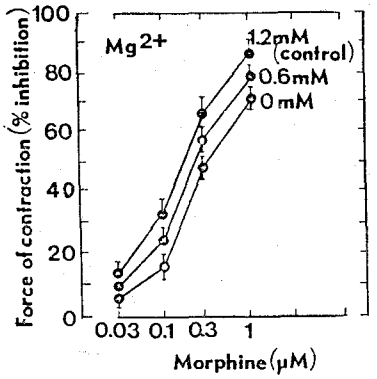


Fig. 5. The effects of $Mg^{2+}$ on the inhibitory action of morphine. See legend to Fig. 2. The concentration of $Na^{+}$ was fixed at 145 mM, and the concentration of $Mg^{2+}$ in the medium was changed as indicated. Each point represents the mean of 6 experiments.

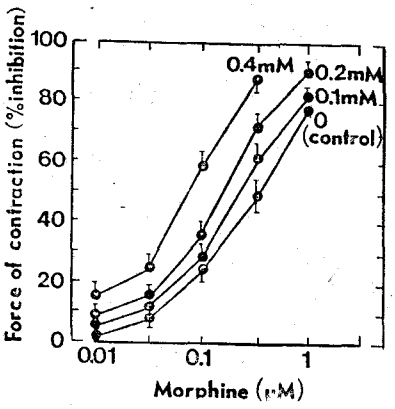


Fig. 6. The effect of $Mn^{2+}$ on the inhibitory action of morphine. See legend to Fig. 2. Preparations were electrically stimulted at 0.2 Hz in a Krebs-Henseleit bicarbonate buffer solution containing indicated concentration of $Mn^{2+}$. Each point represents the mean of 6 experiments.

the concentration of morphine to cause a half-maximal inhibition of the electrically evoked contraction of quinea-pig ilem was sensitive to $Na^{+}$ and contraction of the guinea-pig ileum was sensitive to $Na^{+}$ and $K^{+}$, and the action of morphine was potentiated by lowering either the $Na^{+}$ or $K^{+}$ concentration.

The saturable binding of opiate agonists to

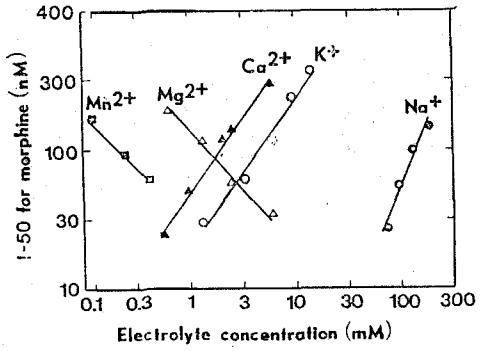


Fig. 7. Effects of various electrolytes on the concentration of morphine to cause a 50 percent inhibition of the contraction of guinea-pig ileum. From data shown in Figs. 2~6, concentrations of morphine to cause a 50 percent inhibition of the evoked contraction (I-50 values) were calculated and plotted against the concentration of 3 electrolytes.

brain homogenates is enhanced by divalent cations such as $Mg^{2+}$, $Mn^{2+}$, $Ni^{2+}$ and $Ca^{2+}$ (Pasternak *et al.*, 1975). Therefore, the effect of these cations on the inhibitory action of morphine was also examined in the isolated guinea-pig ileum. An increase in $Ca^{2+}$ concentration in the medium from 1.8 to 2.7 or 3.6 mM caused a 5.2±1.9% and 9.6±2.0% increase, respectively, in the developed tension, where as a further increase in $Ca^{2+}$ to 7.2 mM resulted in a 3.7±2.2% decrease in developed tension compared to the control value observed in the presence of 1.8 mM $Ca^{2+}$. The increase in $Ca^{2+}$ concentration caused a shift to the right in the concentration-response curve for the inhibitory action of morphine, 7.2 mM $Ca^{2+}$ causing a greater shift than that observed with either 2.7 or 3.6 mM $Ca^{2+}$ (Fig. 4). Thus, the change in force of contraction *per se* is not the primary determinant of the morphine sensitivity of the guinea-pig ileum to $Ca^{2+}$.

A decrease in $Mg^{2+}$ to 0.6 mM or its elim-

ination from the incubation medium caused a 7.9±2.0% and 16.5±4.6% increase in developed tension, respectively, compared to the value observed in the presence of 1.2 mM $Mg^{2+}$; and also shifted the concentration-inhibition curve for morphine to the right (Fig. 5). The addition of 0.1, 0.2 or 0.4 mM $Mn^{2+}$ to the incubation medium caused a 15.2±3.3%, 36.3±2.2% and 42.4±3.8% decrease in developed tension compared to the control value, and potentiated the inhibitory action of morphine on electrically evoked contraction of the guinea-pig ileum (Fig. 6). These results indicate that the effects of increasing divalent cation concentrations in the medium on the potency of morphine to inhibit evoked contractions of guineapig ileum is not uniform; elevated $Mg^{2+}$ or $Mn^{2+}$ concentrations potentiated the inhibitory action of morphine whereas an increase in $Ca^{2+}$ decreased the potency of morphine.

Since various monovalent and divalent cations caused parallel shifts in the concentration-response curves for morphine, it is possible to compare the effects of cations using a single parameter, i.e., the concentration of morphine needed to cause a 50% inhibition of contraction (I-50 value). The plots of I-50 values against logarithmic concentations of cations yielded straight lines (Fig. 7). Increases in $Mn^{2+}$ or $Mg^{2+}$ concentrations decreased I-50 values for morphine, whereas incrased in $Ca^{2+}$ concentration increased the I-50 value. Decreases in $K^+$ on $Na^+$ concentrations decreased the I-50 valuess.

### 3) Effects of naloxone on the inhibitory action of morphine

In order to examine the affinity of the functional opiate receptor for naloxone, the ability of naloxone to antagonize the inhitory action of morphine was estimated (Fig. 8). Naloxone, in concentration from 0.3 to 30 nM, caused a parallel shift in the concentration-response for morphine, consistent with a competitive antagonism. The affinity of the

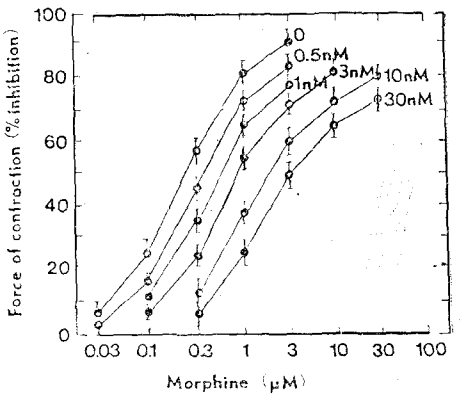


Fig. 8. The antagonistic effect of naloxone on the inhibitory action of morphine. Preparations were electrically stimulated at 0.2 Hz in a modified Krebs-Henseleit bicarbonate buffer solution containing an indicated concentration of naloxone. Aftr equilibration, the inhibitory action of morphine was studied as shown in Fig. 1. Each point represents the mean of 8 experiments. Vertical lines indicate S.E.

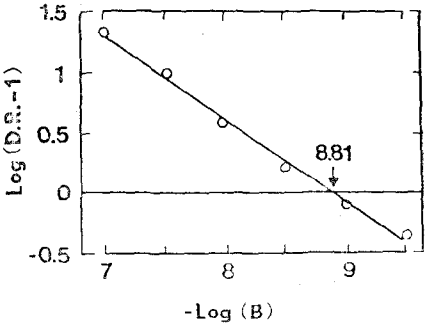


Fig. 9. Determination of $pA_2$ values for naloxone. Dose ratio(DR) for morphine in the presence and absence of naloxone was calculated from Fig. 8, and $\log_{10}(DR-1)$ is plotted against negative logarithm of the molar concentration of naloxone(B). From the intercept of the linear regression line with $\log_{10}(DR-1)=0$, $pA_2$ value was determined.

Table 1. Effects of electrolytes on the $pA_2$ value for naloxone to antagonize the action of morphine.

The $pA_2$ value for naloxone was determined from plots shown in Fig. 9 using data obtained with a modified Krebs-Henseleit bicarbonate buffer solution in which the concentration of one electrolyte was altered as indicated. Numbers in parentheses indicate the concentration of electrolyte in Krebs-Henselelit solution and the $pA_2$ value in control experiments. Each value represents the mean of 6 experiments.

| Electrolyte | | $pA_2$ Value for Naloxone |
|---|---|---|
| | (mM) | (-log M) |
| $Na^+$ | (145) | (8.81) |
| | 125 | 9.05 |
| | 100 | 8.77 |
| | 75 | 8.71 |
| $K^+$ | 2.9 | 8.72 |
| | (5.8) | (8.81) |
| | 8.7 | 8.56 |
| | 11.6 | 8.57 |
| $Ca^{2+}$ | 0.9 | 9.10 |
| | (1.8) | (8.81) |
| | 2.7 | 8.77 |
| | 3.6 | 8.97 |
| $Mg^{2+}$ | 0 | 8.49 |
| | (1.2) | (8.81) |
| | 2.4 | 9.02 |
| | 4.8 | 8.72 |
| $Mn^+$ | (0.0) | (8.81) |
| | 0.05 | 9.01 |
| | 0.1 | 8.68 |
| | 0.2 | 9.05 |
| | 0.4 | 8.67 |

functional opiate recepton for naloxone at which naloxone competitively antagonizes morphine action was estimatad from the apparent $PA_2$ values. From the data shown in Fig. 6, the concentration of morphine which caused a 50% inhibition of electrically evoked contraction in the guinea-pig ileum was calculated for each concentration of naloxone. Subsequently, dose ratios (DR), i., the ratio between I-50 values observed in the presence and absence of naloxone, were calculated and $\log_{10}$ (DR-1) is plotted against $\log_{10}(B)$, where B is the molar concentration of naloxone (Fig. 9), as described by Arunlakshana and Shild (1959) and Takemori (1974). The points were not significantly a linear and the slope of the regression line was slightly shallower, but not significantly different from -1. A linear regression line was fitted by the least square method, and $pA_2$ value was obtained from the intercept of the regression line with $\log_{10}$ (DR-1) = 0. The $pA_2$ value obtained in the medium containing 145 mM $Na^+$ and 5.8 mM $K^+$ was 8.81. This value corresponds to a dissociation constant of 1.55 nM.

Similar experiments were repeated in the medium containg modified $Na^+$, $K^+$, $Ca^{2+}$ or $Mg^{2+}$ concentrations, or that containing $Mn^{2+}$ (Table 1). The electrolyte concentrations were the same as in the Krebs-Henseleit bicarbonate buffer solution except that one ion species was changed as indicated. Again, naloxone caused a parallel shift in the concentration-inhibition curve for morphine in the media containing altered electrolyte concentrations. Alterations in electrolyte concentrations failed to substantially alter the $pA_2$ values for naloxone (These results indicate that the affinity of functional opiate receptors for naloxone is not affected by alterations in either $Na^+$, $K^+$, $Ca^{2+}$ or $Mg^{2+}$ concentration of the medium or by the presence of $Mn^{2+}$.

## DISCUSSION

Morphine causes a concentration-dependent inhibition of the contraction of longitudinal musicle in the ellectrically stimulated guinea-

pig ileum (Cox and Weninstock, 1966; Lees *et al.*, 1973; Kosterltx and Hughes, 1978). In the present study, decreases in either the $Na^+$ or $K^+$ concentration potentiated the inhibitoy action of mophine. The parallel shift in the concentration-inhibition curves for morphine observed with alterd electrolyte concentrations might suggest that electolytes change the affinity of the receptor for morphine. Althougth these data might be explained from the enhanced binding of morphine to its functional receptor in a medium containing a lower $Na^+$ or $K^+$ concentration, various divalent cations which have been shown to enhance opiate agonist binding to saturable binding sites *in vitro* (Pert and Snyder, 1973a; Pasternak *et al.*, 1975) did not cause a consistent change in the inhitory action of morphine; for example, $Mn^{2+}$ and $Mg^{2+}$ potentiated the action of morphine whereas higher concentrations of $Ca^{2+}$ in the incubation medium markedly increased the concentration of morphine required to cause a 50% inhibition of the electrically evoked contraction. Thus, alterations in the potency of morphine to inhibit evoked contractions in the guinea-pig ileum are not likely to result primarily, from changes in the affinity of the saturable binding sites (receptors) for opiate agonist induced by cations.

The effect of altered electrolyte concentrations on the inhibitory action of morphine may result from changes in events which are involved in neurotransmitter release or in the brain and at the neuromuscular junction of peripheral organs (Beleslin and Polak, 1965; Domino and Wilson, 1973; Matthewes *et al.*, 1973; Kosterlitz and waterfield, 1975) This inhibition of acetylholine release has been implicated in the inhibitory action of morphine on the contraction of electrically stimulated guinea-pig ileum (Paton, 1957; Schaumann, 1957; Cox and Weinstock, 1966). The contractile activation as well as the neurotransmitter release involves calcium ions, and therefore various cations, including $Ca^{2+}$ itself, might interfere with these processes. Moreover, the binding opiates to functional reccptors may cause pharmacologcal effects by altering calcium permeability of the cell membrane (Guesseso-Munoz *et al.*, 1979; Harris *et al.*, 1978). If changes in electrolyte concentrations indirectly affect the potency of morphine to inhit the contraction of guinea-pig ileum, then seemingly parallel shifts in contration-response curves for morphine may suggest that only a small fractional occupancy of the functional receptor is required for the inhibitory action of morphine.

The concept that various affect events which are involved in neurotransmitter release or contractile activation, but not the affinity of functional opiate receptors for naloxone is indicated by the lack of a consistent effect on $pA_2$ values. Since $Na^+$ hasb een postulated to decrease the affinity of the opiate receptor for morphine by forcing the receptor to assume an "antagonist" binding configuration (Pert and Snyder, 1973a, 1974; Simon *et al.*, 1973; Snyder, 1975), the lack of changes in $pA_2$ values for naloxone most reasonably indicates no alteration in the affinity of the opiate receptors for morphine.

Since guinea-pig ileum preparations become unstable in a medium containing low concentrations of $Na^+$, experiments could not be per formed with $Na^+$ concentions less than 50 mM. Thus, whether the affinity of functional opiate receptors for morphine or naloxone changes significantly in a medium containing a *very low* concentration of $Na^+$ is unknown. Moreover, the opiate receptors in

guinea-pig ileum could conceivably have properties different from those present in brain homogenates. Although saturable opiate receptor binding has been demonstrated with guinea-pig ileum (Pert and Snyder, 1973b; Creese and Snyder, 1975), the effect of electrolyes on saturable binding has not been thoroughly examined.

In summary, electrolyte concentatious in the medium affect the ability of morphine to inhibit electrically evoked contractions of guinea-pig ileum. Such effects, however, do not appear to be due to electrolyte-induced modification of the functional opiate receptor.

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