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MORPHINE AND APOMORPHINE INHIBIT GASTROINTESTINAL TRANSIT (GIT) THROUGH TWO DIFFERENT MECHANISMS

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ABSTRACT

Morphine was used as a remedy for the control of diarrhea centuries before it's sedative-analgesic effect was discovered.

Although several mechanisms have been proposed for the morphine-induced inhibition of gastrointestinal transit (GIT), the exact mechanism has not yet been identified. On this basis the possible involvement of the dopaminergic system in morphine-induced inhibition of transit was investigated.

This study showed that morphine decreased gastrointestinal transit (GIT) of charcoal dust in mice in a dose-dependent manner. The response was inhibited by the opiate antagonist naloxone. Pretreatment of animals with the D-2 antagonist sulpiride or the peripheral dopamine antagonist domperidone did not alter the morphine-induced inhibition of GIT. The D-1/D-2 agonist apomorphine also decreased GIT in mice. The response was inhibited by SCH 23390 or sulpiride pretreatment ($p<0.01$), but not by domperidone or naloxone. It is concluded that morphine and apomorphine inhibit GIT through opiate and dopaminergic mechanisms, respectively.

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Keywords: Morphine, Dopamine, Gastrointestinal transit.

INTRODUCTION

The constipatory effect of morphine and other opioids is well known.[9] In the past few decades, recognition has developed that opioids can affect gastrointestinal transit through discrete actions in the CNS [4,12] and through local actions on the gut.[10,12,13] The D-1/D-2 agonist apomorphine has also been shown in the rat to reduce the GIT of charcoal meal.[2]

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Increase in the activity of dopamine neurons by morphine[16] and inhibition of dopamine release or turnover by opiopeptides[18] and also influence of dopaminergic systems on the release of opioid in the guinea-pig ileum [11] have all been shown. The involvement of dopaminergic mechanisms in the constipatory effects of morphine and apomorphine have been suggested by Dashmana et al.[2] They showed that the peripheral D-2 dopamine antagonist domperidone antagonizes the inhibitory effects of morphine and apomorphine on the GIT of a charcoal meal in the rat.[2]

Although several mechanisms have been proposed for the morphine-induced inhibition of gastrointestinal transit,[2] the exact mechanism has not yet been identified. On this basis the possible involvement of the dopaminergic system

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in morphine-induced inhibition of transit was investigated in the present study.

MATERIALS AND METHODS

350 male albino mice (20-25g) were used in the study (8 in each group). Animals were housed under standard conditions (22 ±1°C, 8 a.m. /8p.m. light-dark cycle). They were deprived of food, but allowed free access to water for 15 to 18 hr prior to the experiments.

Charcoal meal was composed of charcoal, flour and water in a ratio of 1:2:6. 1 mL of the charcoal meal was administered orally to mice, using a gavage tube based on the Green method.[10]

Table I. Effect of dopamine antagonists on morphine-induced inhibition of gastrointestinal transit (GIT) in mice.

Drug	Dosage (mg/kg)	%GIT (mean ±SEM)
Saline	5 mL	69.0±2.8
Morphine	1	34.7±3.0*
Morphine + SCH 23390	1 0.05	22.2±0.9**
Morphine + SCH 23390	1 0.5	22.3 ±1.0**
Morphine + SCH 23390	1 1	22.4±1.0**
Morphine + Domperidone	1 3	30.5±3.0
Morphine + Domperidone	1 10	31.5 ±1.0
Morphine + Domperidone	1 30	32.5 ±3.0
Morphine + Sulpiride	1 3	34.7±2.0
Morphine + Sulpiride	1 10	33.1 ±2.0
Morphine + Sulpiride	1 50	31.8±2.0

All drugs were injected subcutaneously. Saline and morphine were injected 10 min before charcoal meal administration. SCH 23390, domperidone and sulpiride were injected 20, 15 and 80 min prior to morphine injection, respectively.

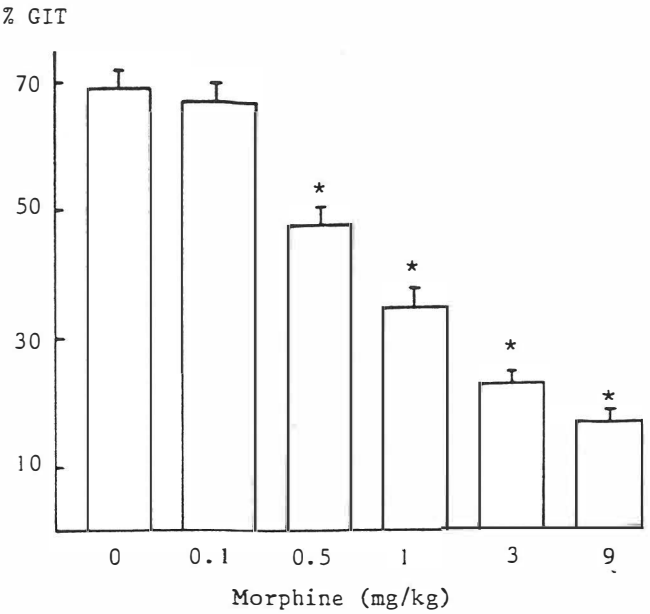


Fig. 1. Effect of morphine on gastrointestinal transit (GIT) in mice. Animals were injected subcutaneously (s.c.) with different doses of morphine (0.1-9 mg/kg) 10 min prior to charcoal administration. Each point is the mean±SEM of 9 mice.

*p<0.01, different from saline treated animals.

The animals were sacrificed by cervical dislocation after 35 min of gavaging. Upon opening the abdomen, the total length of the intestine from the pyloric sphincter to the ileocecal junction was measured. The distance traveled by the charcoal meal from the pyloric sphincter was calculated as the percentage of the intestine's total length and was considered as the GIT percent (% GIT) of each mouse.

Statistical analysis

Statistical evaluation of results was based on ANOVA following the Newman-Keuls test.

Drugs

The following drugs were used: morphine hydrochloride (MacFarlan, England), naloxone and SCH23390 (Research Biochemical Inc., USA), apomorphine hydrochloride, domperidone and sulpiride (Sigma, England). Morphine, naloxone and SCH 23390 were dissolved in normal saline. Apomorphine and domperidone were dissolved in ascorbic acid (0.1%, one drop) and tartaric acid (1%, one drop) respectively and then diluted with normal saline. Sulpiride was dissolved in a drop of glacial acetic acid and then diluted with normal saline. All drugs were injected subcutaneously (s.c.) in a volume of 5 mL/kg.

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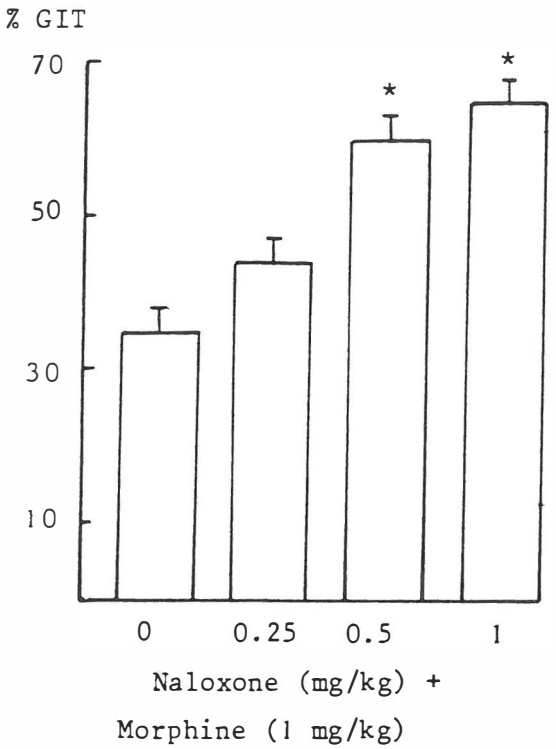


Fig. 2. Effect of different doses of naloxone on morphine response. Mice were pretreated either with saline (5 mL/kg, s.c., 10 min) or naloxone (0.25, 0.5 and 1 mg/kg, s.c., 10 min) before morphine injection. Morphine was administered (1 mg/kg, s.c.) 10 min prior to charcoal employment. Each point is the mean ± SEM of 9 animals.

*p<0.01, different from the morphine (1 mg/kg) group.

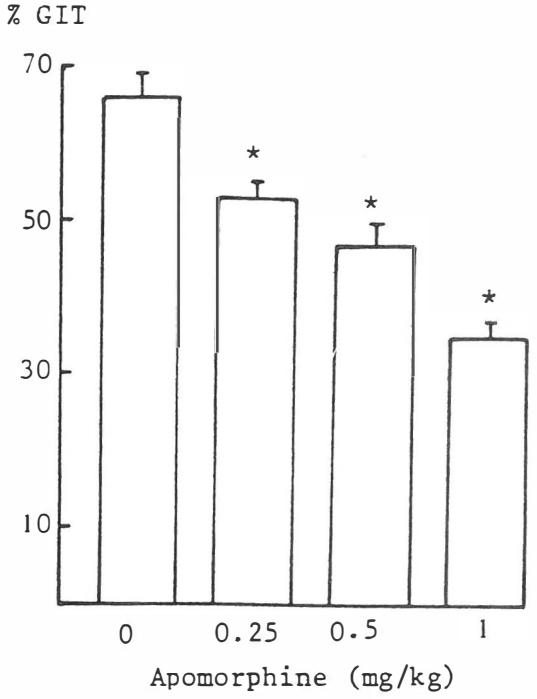


Fig. 3. Effect of apomorphine on GIT in mice. Animals were injected with either vehicle (5 mL/kg, s.c.) or different doses of apomorphine (0.25, 0.5 and 1 mg/kg, s.c.) 20 min before charcoal administration. Each point is the mean ± SEM of 9 animals.

*p<0.01, different from the control group.

RESULTS

Effect of morphine on gastrointestinal transit (GIT) in mice

Different doses of morphine (0.1-9 mg/kg) decreased the GIT of charcoal meal in mice. The response was dose-dependent (Fig.1).

Effect of naloxone and dopamine antagonist on morphine-induced inhibition of GIT

Pretreatment of animals with naloxone (0.25-1 mg/kg, 10 min) reduced the effect of morphine on GIT in mice (Fig. 2). Pretreatment of animals with SCH 23390 (0.05-1 mg/kg, 20 min) but not with sulpiride (3-50 mg/kg, 80 min) or domperidone (3-30 mg/kg, 15 min) increased the morphine response (Table I).

Effect of apomorphine on GIT in mice

Administration of different doses of apomorphine (0.25-1 mg/kg) decreased GIT in a dose-dependent manner (Fig. 3).

Effect of naloxone and dopamine antagonist on apomorphine-induced inhibition of GIT

The inhibitory effect of apomorphine (1 mg/kg) on GIT in mice was decreased in animals pretreated with the D-1 antagonist SCH 23390 (1 mg/kg, 20 min) or the D-2 antagonist sulpiride (50 mg/kg, 80 min), but not by domperidone (30 mg/kg, 15 min) or naloxone (1 mg/kg, 10 min) (Fig. 4).

Effect of naloxone and dopamine antagonists on GIT

Naloxone (0.5, 1 and 2 mg/kg), sulpiride (50-80 mg/kg) and domperidone (1-30 mg/kg) 10, 80 and 15 min before the charcoal meal respectively, did not change the GIT. However, SCH 23390 (0.01, 0.05, 0.5 and 1 mg/kg) 20 min prior to administration of charcoal meal, decreased the GIT as compared with control animals (Table II).

DISCUSSION

It is generally accepted that morphine reduces GIT. This effect has been attributed to central,[4,13] peripheral,[10,13,14] or both central and peripheral mechanisms.[17]

The D-1/D-2 agonist apomorphine has also been shown to reduce GIT.[2]

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Table II. Effect of naloxone and dopamine antagonists on GIT.

Drug	Dosage (mg/kg)	%GIT (Mean±SEM)
Saline	5 mL	69.0±3.0
Naloxone	0.5	69.0±3.0
Naloxone	1	61.6±2.0
Naloxone	2	60.6±3.0
SCH 23390	0.01	60.2±2.0*
SCH 23390	0.05	60.6±2.0*
SCH 23390	0.5	60.6±2.8*
SCH 23390	1	61.2±1.8*
Vehicle	5 mL	68.4±3.0
Domperidone	1	66.6±3.0
Domperidone	3	69.3±3.0
Domperidone	30	66.8±3.0
Vehicle	5 mL	65.0±3.0
Sulpiride	50	64.9±3.0
Sulpiride	80	61.0±3.0

Naloxone, SCH 23390, domperidone and sulpiride were injected (s.c.) 10, 20, 15 and 80 min before charcoal meal administration, respectively. Each point is the mean±SEM of at least 8 mice. *$p<0.05$, different from the control group.

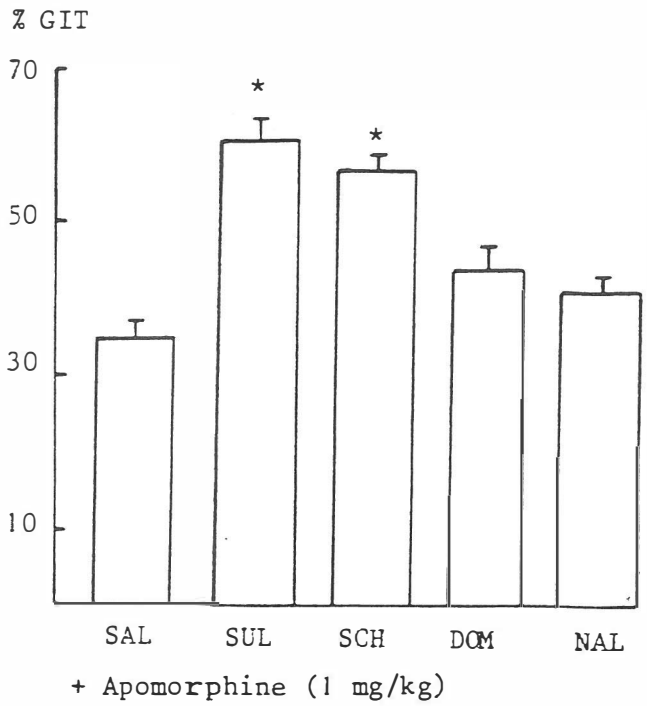


Fig. 4. Effect of naloxone and dopamine antagonists on apomorphine-induced inhibition of GIT in mice. Animals were injected with apomorphine (1 mg/kg, s.c.) alone, 20 min before charcoal meal administration, or sulpiride (50 mg/kg, s.c.) 80 min, SCH 23390 (1 mg/kg, s.c.) 20 min, domperidone (30 mg/kg, s.c.) 15 min, or naloxone (1 mg/kg, s.c.) 10 min prior to apomorphine injection.
*$p<0.01$, different from the apomorphine (1 mg/kg) group. Each point is the mean±SEM of 8 animals.
*$p<0.01$, different from saline treated mice.
**$p<0.01$, different from morphine treated animals.

Dopamine functions through at least two different D-1 and D-2 receptor sites.[7] We used the mice charcoal meal test for comparing the constipatory actions of morphine with that of apomorphine. In our study both morphine and apomorphine decreased GIT in mice. The effect of morphine was reversed by the opiate antagonist naloxone. The D-2 antagonist sulpiride[15] and the peripheral dopamine antagonist domperidone[8] did not inhibit the morphine response. These data may indicate that the inhibitory effect of morphine on GIT is effected through opiate but not dopaminergic mechanisms. Therefore our results are in contradiction with the results of Dashmana et al,[2] suggesting that the decrease in GIT by morphine may be mediated via the dopaminergic system in the rat; although difference in species of animals should also be considered.

The D-1 antagonist SCH 23390[6] not only decreased but also increased the effect of morphine. SCH 23390 has been shown to have the ability to induce a 5-HT receptor stimulatory effect, although 5-HT receptor activation may elicit contraction of intestinal circular muscle in the rat.[1] Administration of SCH 23390 alone also decreases GIT. Therefore the increase in morphine's effect may reflect this response of SCH 23390, however other mechanisms are not excluded. The D-1/D-2 agonist apomorphine also decreases GIT. Both the D-1 antagonist SCH 23390 and the D-2 antagonist sulpiride reduced the effect of apomorphine, which may indicate the involvement of dopaminergic mechanisms in the response. Our results confirm those obtained by others[2,12] in this respect. However, the peripheral dopamine antagonist domperidone did not alter apomorphine's action. This may show that the effect of apomorphine is induced through a central dopaminergic mechanism.

Failure of naloxone pretreatment to inhibit the apomorphine effect excluded the opiate mechanism in the apomorphine response. Overall the data may show that morphine and apomorphine induce a decrease in GIT of charcoal meal through two different mechanisms. Further studies are required to prove this hypothesis.

REFERENCES

1. Burks TF: Acute effects of morphine on rat intestinal motility. Eur J Pharmacol 40:279-283, 1976.
2. Dashmana KM, Banerjee AK, Zhu YN, Erdmann W: Role of dopamine receptors in gastrointestinal motility. Res Commun Chem Pathol Pharmacol 64: 485-488, 1989.

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3. Eaker EY, Bixler GB, Dunn AJ, Morshead WV, Mathias JR: Dopamine and norepinephrine in the gastrointestinal tract of mice and the effects of neurotoxins. J Pharmacol Exp Ther 244: 438-442, 1988.
4. Galligan JJ, Burks TF: Centrally mediated inhibition of small intestinal transit and motility by morphine in the rat. J Pharmacol Exp Ther 226: 356-361, 1983.
5. Glavin GB, Szabo S: Dopamine in gastrointestinal disease. Digestive Disease and Sciences 35: 1153-1161, 1990.
6. Hyttel J: Functional evidence for selective dopamine D-1 receptor blockade by SCH 23390. Neuropharmacology 23: 1395-1401, 1984.
7. Kebabian J, Calne DB: Multiple receptors for dopamine. Nature 277: 93-96, 1979.
8. Kilbinger H, Weihrauch TR: Drugs increasing gastrointestinal motility. Pharmacology 25: 61-72, 1982.
9. Latasch L, Zimmermann M, Eberhardt B, Jurna I: Treatment of morphine-induced constipation with oral naloxone. Anaesthesist 46(3): 191-4, 1997.
10. Manara L, Bianchi G, Ferretti P, Tavani A: Inhibition of gastrointestinal transit by morphine in rats results primarily from direct drug action on gut opioid sites. J Pharmacol Exp Ther 237: 945-947, 1986.
11. Milanes MV, Martinez JA, Vargas ML: Influence of dopaminergic and noradrenergic systems on the release of opioid peptides in guinea-pig ileum. J Pharm Pharmacol 41: 607-611, 1989.
12. Naito Y, Kuzuhara S: Parkinsonism induced or worsened by cisapride. Nippon-Ronen-Igakkai-Zasshi 31 (11): 899-902, 1994.
13. Shook JE, Pelton JT, Hruby VJ, Burks TF: Peptide opioid antagonist separates peripheral and central opioid antitransit effects. J Pharmacol Exp Ther 243: 492-500, 1987.
14. Stewart JJ, Weisbrodt NW, Burks TF: Central and peripheral actions of morphine on intestinal transit. J Pharmacol Exp Ther 205: 547-555, 1978.
15. Stoof JC, Kebabian JW: Two dopamine receptors: biochemistry, physiology and pharmacology. Life Sci 35: 2281-2296, 1984.
16. Trulson ME, Arasteh K: Morphine increases the activity of midbrain dopamine neurons *in vitro*. Eur J Pharmacol 114: 105-109, 1985.
17. Ward SJ, Takemori AE: Relative involvement of receptor subtypes in opioid-induced inhibition of gastrointestinal transit in mice. J Pharmacol Exp Ther 224: 359-363, 1983.
18. Yonehara N, Clouet DH: Effects of delta and mu opiopeptides on the turnover and release of dopamine in rat striatum. J Pharmacol Exp Ther 231: 38-42, 1984.

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