Effects of Adrenalectomy on Pharmacokinetics and Antinociceptive Activity of Morphine in Rats

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Abstract—The effects of adrenalectomy on the pharmacokinetics and antinociceptive activity of morphine were investigated to elucidate the mechanism of adrenalectomy-induced potentiation of morphine antinociception in rats. Plasma concentrations of morphine were estimated specifically and serially in each rat by high performance liquid chromatography with an electrochemical detector. After the intravenous administration of 10 mg/kg morphine, the plasma half-life of morphine was significantly prolonged by adrenalectomy without any effect on the volume of morphine distribution. After the subcutaneous administration of 7 mg/kg morphine, pharmacokinetic parameters were changed by adrenalectomy in the same manner as after intravenous administration. In contrast, after the subcutaneous injection of 3.5 mg/kg morphine, adrenalectomy failed to change the pharmacokinetic parameters. The antinociceptive potency of subcutaneously administered morphine was enhanced by adrenalectomy for both doses of morphine (3.5 and 7 mg/kg). Morphine antinociception at the dose of 3.5 mg/kg, s.c., in the adrenalectomized group was equipotent with that of 7 mg/kg, s.c., in the sham-operated group, but plasma morphine concentrations for 3.5 mg/kg, s.c., in the adrenalectomized group were significantly lower than those for 7 mg/kg morphine, s.c., in the sham-operated group. These results suggest that the enhancement of morphine antinociception by adrenalectomy cannot be explained by the increased morphine level alone.

Previous studies (1–5) have indicated that adrenalectomy potentiates the antinociceptive activity of systemically administered morphine in rats. With respect to the mechanism of adrenalectomy-induced enhancement of morphine antinociception, Holaday et al. (3, 4) reported that adrenalectomy failed to alter the analgesic potency of intracerebroventricularly administered morphine, but enhanced that of subcutaneously administered morphine. They suggested from those results that adrenalectomy causes a decrease in morphine metabolism which enhances morphine analgesia through an increased morphine level with no change in the sensitivity to morphine. On the other hand, Lewis et al. (6) suggested that adrenalectomy may potentiate opiate analgesia by increasing the affinity of opiate receptors in response to the loss of adrenocortical hormones. At present, the mechanism of adrenalectomy-induced enhancement of morphine analgesia remains to be elucidated.

In the present study, we examined the effects of adrenalectomy on the pharmacokinetics of plasma morphine and morphine analgesia, and attempted to determine whether the enhancement of morphine antinociception could be explained by the increased morphine level alone.

Materials and Methods

Male Sprague-Dawley rats (Clea, Japan) weighing 300–400 g were used in these experiments. They were housed in pairs in hanging wire cages in air-conditioned (23–24°C), light-controlled (lights on from 08:00 to 20:00) room. Food (CA-1, Clea, Japan) and water were available ad libitum. Adrenalectomy or sham operations were per-
formed by bilateral dorsal incisions under ether anesthesia. Adrenalectomized rats were given 0.9% NaCl as drinking water.

**Pharmacokinetic study:** Animals implanted with jugular cannulas according to the Upton method (7) on the 5th day after adrenalectomy or sham operation were then individually housed and used in pharmacokinetic studies performed on the 8th day after adrenalectomy or sham operation. In the intravenous study, 10 mg/kg morphine was administered through the jugular cannula; and blood samples of 0.2, 0.2, 0.2, 0.4, 0.4 and 1 ml were collected through the cannula at 10, 30, 60, 90, 120 and 180 min after administration, respectively. In the subcutaneous study, morphine at the dose of 3.5 or 7 mg/kg was administered subcutaneously; and blood samples of 0.2, 0.2, 0.2, 0.4, 0.4 and 1 ml were collected through the jugular cannula at 15, 30, 45, 60, 90 and 120 min after administration, respectively. Blood samples were centrifuged at 2000×g for 15 min at 4°C, and the plasma was stored at -80°C until morphine determination. Pharmacokinetic parameters from the plasma concentration-time curves were calculated by the least squares method according to the one-compartment open model (8).

**Antinociceptive study:** Animals without cannulation were used in the morphine antinociceptive study on the 8th day after adrenalectomy or sham operation. These animals were gently handled for at least 5 days prior to the experiment to accustom them to the experimental procedures. The hind-paw pressure method (9) with an analgesy-meter (Ugo Basile) was used to estimate the behavioral pain threshold. Basal pain threshold was measured twice, at an interval of 10 min, just before morphine administration. Pain thresholds were measured every 10 min for 120 min after morphine administration (3.5 or 7 mg/kg, s.c.). When the weight load on the hind-paw exceeded 1750 g, the pain threshold was determined to be 1750 g.

**Determination of morphine by HPLC-ECD method:** Plasma morphine was determined by high performance liquid chromatography (HPLC) with an electrochemical detector (ECD). Plasma samples (0.1–0.5 ml) were brought to a total volume of 1 ml by adding H$_2$O, buffered with 1 ml of 40% K$_2$HPO$_4$ solution, shaken with 5 ml of ethylacetate for 20 min at room temperature, and then centrifuged at 2000×g for 5 min at 4°C. The organic layer was collected, and the aqueous layer was re-extracted with 5 ml of ethylacetate, as described above. The organic layer was pooled and evaporated to dryness under an air stream by a rotary evaporator at 40°C. The dried sample was then dissolved in 200 µl of methanol, and 50 µl aliquots were injected into the HPLC-ECD system. HPLC conditions were as follows: column, Radial pak A (C$_{18}$) and RCM-100 (Waters); mobile phase, 0.05 M ammonium acetate/acetonitrile (80/20); flow rate, 2 ml/min; ECD 0.7 V Ag/AgCI (VMD-101, Yanagimoto); chart speed, 0.5 cm/min.

**Drugs and statistical analysis:** Chemicals used were as follows: morphine hydrochloride (Takeda Pharm.), K$_2$HPO$_4$ and ammonium acetate (special grade, Katayama Chem.), ethyl acetate, methanol and acetonitrile (HPLC-grade, Katayama Chem.). Doses and plasma concentrations of morphine were calculated as morphine hydrochloride. Statistical comparisons were done by the two-tailed Student’s t-test.

**Results**

**Determination of morphine by HPLC-ECD method:** The HPLC chromatogram of the plasma sample showed that the morphine peak was clearly separated from the other peaks (Fig. 1). The peak height of the morphine chromatogram gave a linear calibration curve of at least 1–200 ng of morphine. Recoveries from the extraction and detection procedures were found to be 90.0±4.3% (mean±S.D., n=16) when 20–200 ng of morphine was added to 0.5 ml of intact rat plasma. When 0.5 ml of plasma sample was used, about 4 ng/ml of plasma morphine was detectable.

**Pharmacokinetics after intravenous administration:** Plasma concentrations of morphine were estimated for 180 min after intravenous injection of 10 mg/kg of morphine. The semilogarithmic disappearance curves of morphine are shown in Fig. 2. Although there was no difference in the
plasma morphine levels at 10 min after administration between adrenalectomized and sham-operated groups, the plasma morphine levels in the adrenalectomized group at 30-180 min after administration were significantly higher than those in the sham-operated group.

Pharmacokinetic parameters after intravenous morphine administration are shown in Table 1. Apparent volume of distribution (Vd) was not influenced by adrenalectomy, but there was a significant prolongation in plasma half-life (t(1/2)) with adrenalectomy, which resulted in a significant increase in the area under the concentration-time curve (AUC) and a significant decrease in total

![Authentic Morphine vs Plasma Morphine](image)

**Fig. 1.** Typical chromatograms obtained from authentic morphine (20 ng) and plasma sample at 90 min after morphine, 3.5 mg/kg, s.c. For HPLC-ECD conditions see Methods.

![Plasma Morphine Concentration-Time Curves](image)

**Fig. 2.** Plasma concentration-time curves of morphine following intravenous administration of morphine (10 mg/kg). The ordinate represents morphine concentration on a logarithmic scale. Each point and vertical bar represent the mean and S.E. from sham-operated (n=6) and adrenalectomized (n=9) rats. Differs from the sham-operated group, *P<0.05, **P<0.01. Abbreviations: SHAM, sham-operated group; ADX, adrenalectomized group.

| Table 1. Pharmacokinetic parameters of morphine after intravenous administration of 10 mg/kg |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Treatment (n) | t(1/2) (min) | Vd (l/kg) | AUC (µg·min/ml) | Clearance (ml/kg/min) |
|----------------|--------------|----------|-----------------|----------------------|
| SHAM (6) | 31.4±4.1    | 2.87±0.19 | 1.63±0.25 | 72.5±15.7           |
| ADX (9) | 60.5±5.1*   | 2.45±0.28 | 3.17±0.32*** | 35.1±4.7*           |

Each data represents the mean±S.E. calculated by the least squares method according to the one compartment open model. Differs from the sham-operated group, *P<0.05, **P<0.01. Abbreviations: t(1/2), plasma half-life; Vd, apparent volume of distribution; AUC, area under the concentration-time curve; Clearance, total plasma clearance.
plasma clearance (Clearance).

**Pharmacokinetics after subcutaneous administration:** Plasma concentrations of morphine were estimated for 120 min after the subcutaneous injection of 3.5 or 7 mg/kg of morphine. The semilogarithmic disappearance curves of morphine are shown in Fig. 3. In the case of 7 mg/kg morphine, plasma morphine levels in the adrenalectomized group were significantly higher than those in the sham-operated group throughout the experiment. In contrast, with 3.5 mg/kg morphine, there was no significant difference in plasma morphine levels between the adrenalectomized and sham-operated groups throughout the experiment. Plasma morphine levels following administration of 3.5 mg/kg morphine, s.c., in the adrenalectomized group were significantly lower than those for 7 mg/kg morphine, s.c., in the sham-operated group at 15–45 min after administration.

**Pharmacokinetic parameters after subcutaneous morphine administration are shown in Table 2.** The effects of adrenalectomy on the pharmacokinetic parameters after 7 mg/kg morphine, s.c., were almost the same as those after intravenous morphine administration (10 mg/kg). i.e., adrenalectomy did not influence \( V_d \), but significantly prolonged \( t(1/2) \), increased AUC and decreased Clearance. In contrast, pharmacokinetic parameters after the administration of 3.5 mg/kg morphine, s.c., were not changed significantly by adrenalectomy.

**Antinociceptive study after subcutaneous administration of morphine:** Pain thresholds were measured for 120 min after the subcutaneous injection of 3.5 or 7 mg/kg of morphine (Fig. 4). Basal pain threshold was not significantly changed by adrenalectomy: 73.8±6.9 g (mean±S.E., n=8) in the sham-operated group and 91.9±5.0 g (mean±S.E., n=8) in the adrenalectomized group. The time course of morphine antinociception was not influenced by adrenalectomy. The antinociceptive potency of morphine was enhanced by adrenalectomy at both doses of morphine. The antinociceptive effect of 3.5

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**Table 2. Pharmacokinetic parameters of morphine after subcutaneous administration of 3.5 or 7 mg/kg**

| Treatment | (n) | \( t(1/2) \) (min) | \( V_d \) (l/kg) | AUC (\( \mu g \cdot \text{min} / \text{ml} \)) | Clearance (ml/kg/min) |
|-----------|-----|---------------------|-----------------|---------------------------------|----------------------|
| Mor 3.5   | SHAM (7) | 41.2±4.5           | 8.16±1.55       | 28.1±2.8                        | 133±14               |
|           | ADX (8)  | 48.4±3.6           | 8.10±0.94       | 33.4±4.7                        | 122±19               |
| Mor 7     | SHAM (8) | 30.6±2.2           | 6.28±0.72       | 52.3±6.8                        | 160±30               |
|           | ADX (7)  | 51.4±4.9**         | 5.56±1.41       | 117.5±19.4**                    | 72±14**              |

Each data represents the mean±S.E. calculated by the least squares method according to the one compartment open model. Differences from the sham-operated group at each dose, *\( P<0.05 \), **\( P<0.01 \). For abbreviations, see the legends for Table 1 and Fig. 3.
mg/kg morphine, s.c., in the adrenalectomized group was almost equi-analgesic to that of 7 mg/kg morphine in the sham-operated group.

Discussion

Although previous studies (1-5) have established that adrenalectomy potentiates the antinociceptive activity of systemically administered morphine in rats, the mechanism of this effect has not been elucidated. Possible mechanisms for the enhancement of morphine action may be as follows: [1] an increased morphine level at the opiate receptor site, which may be caused by increased absorption of morphine, decreased metabolism and/or elimination of morphine, decreased volume of morphine distribution, or increased passage of morphine into the central nervous system or [2] increased sensitivity to morphine, which may be caused by an increased number of opiate receptors, increased affinity of the opiate receptors to morphine, or increased efficacy of morphine activity in some sites of action.

Holaday et al. (3, 4) reported that adrenalectomy failed to alter the potency of intracerebroventricularly administered morphine, but enhanced that of systemically administered morphine, and they also reported that adrenalectomy increased the morphine levels in blood and brain, thus supporting the former possible mechanism resulting from a decrease in morphine metabolism. However, in their study, morphine was estimated by the total radioactivity of tritium after the intravenous injection of tritium-morphine at only one time point after administration.

In the present study, we estimated plasma morphine specifically and serially in each individual rat, and the effects of adrenalectomy on the plasma pharmacokinetics of morphine after intravenous and subcutaneous administrations were investigated. Although morphine is eliminated from plasma in a multi-compartmental fashion (10, 11), the one-compartment model was used conveniently for the comparison of pharmacokinetic parameters.

First, the effects of adrenalectomy on the plasma pharmacokinetics of morphine after intravenous administration which does not include the absorption process were investigated. Although there was no difference in the plasma morphine levels at 10 min after administration between the adrenalectomized and the sham-operated groups, the plasma morphine levels in the adrenalectomized group were significantly higher than those in the sham-operated group at 30–180 min after administration (Fig. 2), and the analysis of pharmacokinetic parameters revealed that the volume of morphine distribution was not affected but the plasma half-life of morphine was prolonged by adrenalectomy (Table 1). These results suggest that adrenalectomy reduces morphine metabolism, consistent with the results of Holaday et al. (4).

Next, we investigated the effects of adrenalectomy on the plasma pharmacokinetics of morphine after subcutaneous adminis-
tration which includes the absorption process. The two doses of morphine (3.5 and 7 mg/kg) were chosen based on the preliminary study suggesting that the analgesic potency of 3.5 mg/kg, s.c., in adrenalectomized rats was equipotent with that of 7 mg/kg, s.c., in sham-operated rats. This study provided us with interesting results. After 7 mg/kg morphine, s.c., the plasma morphine levels were significantly increased by adrenalectomy throughout the experiment (Fig. 3), and the pharmacokinetic parameters were changed by adrenalectomy in the same manner as in the intravenous study; i.e., adrenalectomy significantly prolonged the plasma half-life of morphine with no change in the volume of morphine distribution (Table 2). The result that the volume of distribution was not changed by adrenalectomy both after subcutaneous and intravenous administration suggests that the absorption and the distribution volume of morphine are not changed by adrenalectomy, consistent with the data of Adler et al. (12). The prolongation of plasma half-life of morphine by adrenalectomy both after subcutaneous and intravenous administration suggests that adrenalectomy reduces the morphine metabolism. However, with the low dose of morphine (3.5 mg/kg, s.c.), although a tendency for adrenalectomy to prolong the plasma half-life of morphine was observed, no significant differences in the plasma morphine levels and the pharmacokinetic parameters between sham-operated and adrenalectomized rats were observed (Fig. 3 and Table 2).

The fact that the decrease in morphine metabolism was manifested as an increase in plasma morphine level and prolongation of plasma half-life of morphine after high dose of morphine but not after low dose may suggest that the adrenalectomy-induced decrease in the capacity of morphine metabolism is still sufficient for the metabolism of 3.5 mg/kg morphine, s.c., but not for those of morphine at 7 mg/kg, s.c. or 10 mg/kg, i.v. This result agreed with those of Adler et al. (12) who reported that the adrenalectomy-induced increase in morphine levels was more pronounced at 5 mg/kg morphine than at 2 mg/kg morphine.

Although the activity of mixed function oxidase in liver microsomes is known to be reduced by adrenalectomy (13–15), there have been contradictory reports about the effect of adrenalectomy on the activity of glucuronidation, which is the main route of morphine metabolism. Adler et al. (12) and Way et al. (16) suggested that adrenalectomy does not reduce the ability to conjugate morphine. On the other hand, Zauder (17) reported that in vitro conjugation of morphine does not occur with the liver slices obtained from adrenalectomized rats, and Holaday et al. (4) suggested that adrenalectomy-induced decrease in morphine metabolism might be due to the reduced protein synthesis of a functional component of the morphine metabolizing system. It may be possible that adrenalectomy reduces the ability of the conjugation of morphine, because both the ability of morphine glucuronidation and the activity of mixed function oxidase are stimulated by drug metabolizing enzyme inducers and are reduced by SKF 525-A (18, 19). The precise mechanism involved in the adrenalectomy-induced reduction of morphine metabolism remains to be elucidated.

The antinociceptive potency of subcutaneously administered morphine was enhanced by adrenalectomy at both morphine doses (3.5 and 7 mg/kg), and the time courses of morphine effects following both doses were not affected by adrenalectomy. As the antinociceptive effect of 3.5 mg/kg morphine, s.c., in adrenalectomized rats was almost the same as that of 7 mg/kg morphine, s.c., in the sham-operated rats, morphine antinociception was enhanced about two-fold by adrenalectomy. The degree of the enhancement of morphine antinociception induced by adrenalectomy was consistent with the results of other investigators (1–5).

The antinociceptive effect of 3.5 mg/kg morphine, s.c., was potentiated by adrenalectomy without any change in plasma morphine concentration. Furthermore the plasma morphine levels after 3.5 mg/kg morphine, s.c., in the adrenalectomized group were significantly lower than those after 7 mg/kg morphine, s.c., in the sham-operated group at 15–45 min after morphine administration. As those groups were equi-analgesic, morphine should produce equi-analgesia with significantly lower plasma morphine levels in
adrenalectomized rats compared with sham-operated rats. In the present study, the morphine contents in the central nervous system were not measured, so the possibility that adrenalectomy increases the passage of morphine through the blood brain barrier (20) or the blood cerebrospinal fluid barrier cannot be excluded. However, judging from the data of Adler et al. (12) and Holaday et al. (4), the morphine content ratios, i.e., brain/plasma and spinal/plasma, are unlikely to be increased by adrenalectomy. Thus these results suggest that adrenalectomy increases the sensitivity to morphine.

The antinociceptive effect of 7 mg/kg morphine, s.c., was potentiated by adrenalectomy accompanying a significantly increased plasma morphine level. Does this potentiation of 7 mg/kg morphine antinociception result from an increase in plasma morphine level or an increase in the sensitivity to morphine? In sham-operated rats, the intensity of antinociception of 7 mg/kg morphine (area under analgesic curve; AUAC=87 kg x min, Fig. 4) was 1.8 times more potent than that of 3.5 mg/kg morphine (AUAC=49 kg x min, Fig. 4), while AUC after 7 mg/kg morphine (52 μg x min/ml, Table 2) was 1.9 times of that after 3.5 mg/kg morphine (28 μg x min/ml, Table 2). The intensity of 7 mg/kg morphine antinociception in adrenalectomized rats (AUAC=146 kg x min, Fig. 4) was 1.7 times more potent than that in sham-operated rats, while AUC in the adrenalectomized group (118 μg x min/ml, Table 2) was 2.3 times of that in the sham-operated group. Then the adrenalectomy-induced increase in AUC after 7 mg/kg morphine, s.c., could be sufficient for the adrenalectomy-induced potentiation of 7 mg/kg morphine antinociception. However at the same time, the increase in the sensitivity to morphine must be produced by adrenalectomy regardless of the morphine dose. Therefore, both the increase in plasma morphine level and the increase in the sensitivity to morphine might be involved in the adrenalectomy-induced potentiation of 7 mg/kg antinociception, but it was impossible to estimate from the present results the relative roles of the increased morphine level and the increased sensitivity to morphine in the enhancement of morphine analgesia.

Possible mechanisms for the increased sensitivity to morphine may be as follows: increased number of opiate receptors, increased affinity of the opiate receptors to morphine (for example, decreased Na⁺ ion level at opiate receptor site (21)) or increased efficacy of morphine activity in some sites of action (for example, the descending inhibitory systems (22, 23) and/or the interaction between spinal and supraspinal morphine action (24)). Lewis et al. (6) discussed that adrenalectomy potentiates opiate analgesia by increasing the affinity of opiate receptors for opiate drugs, but the analgesia induced by intracerebroventricular morphine was not potentiated by adrenalectomy (3). Although adrenal steroids play an important role in the regulation of electrolytes, especially Na⁺ and K⁺ (25), it is considered that mineralcorticoid properties are not necessary to reverse the adrenalectomy-induced potentiation of morphine analgesia (4). It has been reported that adrenal demedullation or adrenal denervation does not affect morphine analgesia (6), so the removal of adrenal medulla may not be involved in the adrenalectomy-induced increase in the sensitivity to morphine. The mechanism of the adrenalectomy-induced increase in the sensitivity to morphine remains to be elucidated.

In summary, the decrease in morphine metabolism and increase in plasma morphine concentration with adrenalectomy were observed only after the high dose of morphine. Morphine antinociception at the low dose (3.5 mg/kg, s.c.) was potentiated by adrenalectomy with no detectable change in plasma morphine concentration. The plasma concentration of morphine producing the equi-antinociceptive effect was lower in adrenalectomized rats than in sham-operated rats. These results indicate that the adrenalectomy-induced enhancement of morphine antinociception can not be explained by increased morphine level alone, suggesting that another mechanism, i.e., increased sensitivity to morphine, is involved.

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