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INCREASED SENSITIVITY OF THE CENTRAL NERVOUS SYSTEM TO MORPHINE ANALGESIA BY AMITRIPTYLINE IN NAIVE AND MORPHINE-TOLERANT RATS

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Abstract—The effects of amitriptyline (AT) (20 mg/kg, i.p.), given 1 hr before [^{14}C]morphine administration, on the analgesic response and tissue distribution of [^{14}C]morphine and [^{14}C]morphine glucuronide (MG) were studied in naive and morphine-tolerant rats. Rats were rendered tolerant to morphine analgesia by s.c. implantation for 3 days of a pellet containing 75 mg of morphine base. In naive rats, AT treatment increased the intensity and prolonged the duration of morphine analgesia. Amitriptyline treatment did not cause any significant change in the concentrations of [^{14}C]morphine in the brain or of total ^{14}C in the plasma 30, 60 and 90 min after administration of [^{14}C]morphine. With the exception of a slight increase in total ^{14}C in the liver at 30-min, AT treatment did not affect the concentrations of total ^{14}C in the liver and urine. The fact that the percentages of total ^{14}C in the liver or urine as [^{14}C]MG were not changed by AT treatment suggests that AT did not affect biotransformation of morphine. This suggestion was supported by our previous report that a metabolic drug interaction with morphine would be reflected by a change in the percentage of total ^{14}C as [^{14}C]MG in the liver and urine [S. J. Liu and R. I. H. Wang, *Drug Metab. Dispos.* **8**, 260 (1980)]. Potentiation of morphine analgesia, similar to that seen in naive rats, was also found in morphine-tolerant rats. The brain concentration of [^{14}C]morphine in AT-treated morphine-tolerant rats at 60-min was lower than that in controlled morphine-tolerant rats. However, the concentrations of total ^{14}C in liver and urine and the percentage of total ^{14}C in liver or urine as [^{14}C]MG were not changed significantly by AT treatment in morphine-tolerant rats. It was concluded that AT treatment prolonged morphine analgesia by increasing the sensitivity of the central nervous system to morphine rather than by changing morphine pharmacokinetics.

Trycyclic antidepressants have been shown to interact, by several mechanisms, with a variety of compounds including barbiturates [1, 2], monoamine oxidase inhibitors [3, 4], and several other central nervous system (CNS) stimulants and depressants [5, 6]. With respect to interactions between tricyclic antidepressants and narcotic analgesics, imipramine has potentiated morphine analgesia in mice as measured by tail clip and electric shock analgesic tests [7]. Imipramine and desipramine have been shown to increase morphine analgesia in rabbits, as measured by the dental pain method [8]. These two tricyclic antidepressants have also enhanced meperidine-induced respiratory depression in man [9]. We have shown that desipramine potentiated methadone analgesia in naive and methadone-tolerant rats [10, 11], and that it enhanced methadone toxicity in naive rats [10].

There are several situations in which morphine is used in combination with tricyclic antidepressants. The concomitant use of these medications creates the possibility of drug interactions that may, in turn, result in an alteration of the pharmacological effects of morphine. The present studies were undertaken to investigate the effect of amitriptyline (AT) on the analgesic response to morphine and the possible mechanism(s) involved. Amitriptyline was chosen as a model of tricyclic antidepressants for these studies since we previously demonstrated that, among the tricyclic antidepressants, AT most markedly increased CNS sensitivity to barbital [1].

Long-term administration of morphine is utilized for certain therapeutic purposes, and the development of tolerance to morphine is a well-established phenomenon. Therefore, we also investigated the effect of AT on morphine analgesia in morphine-tolerant rats and compared the results with those in naive animals.

MATERIALS AND METHODS

Animals and chemicals. Male Sprague–Dawley rats (Spartan Research, Haslett, MI), weighing 120–160 g, were used throughout these studies. The rats were fed Purina Laboratory Chow and water *ad lib.* under a 12-hr light–dark cycle in temperature-controlled animal quarters. Morphine sulfate and [*N*-methyl-^{14}C]morphine hydrochloride were purchased from Mallinckrodt Chemical Works (St. Louis, MO) and the Amersham Corp. (Arlington Heights, IL) respectively. The [^{14}C]morphine had a

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94 per cent radiochemical purity, as checked by thin-layer chromatography. The [*N*-methyl-^{14}C]morphine glucuronide (MG) standard was obtained from Dr. James M. Fujimoto of this VA Medical Center. Amitriptyline hydrochloride was supplied by Merck & Company, Inc. (Rahway, NJ).

The ^{14}C-labeled and nonlabeled morphine were mixed in saline to establish a specific activity of 1 or 2 μCi/mg. For the tissue distribution study, animals were given 20 μCi of radioactivity per kg of body weight. Doses of drugs will be expressed hereafter in terms of their salts. Solutions of morphine and AT were administered via s.c. and i.p. routes respectively. The injection volume was 2.0 ml/kg. Control rats received an equivalent volume of saline.

Determination of analgesia. Analgesia was measured by the modified hot plate method of Eddy and Leimbach [12], as described previously [10]. The surface temperature of the plate (TLI Thermajust Analgesia Meter, Technilab Instrument, Inc., Pequannock, NJ) was maintained at 58 ± 0.5° throughout the experiment. A standard 30-sec cutoff time, as used by other investigators [12, 13], was used as a maximal analgesic effect for studying the time–response curves of morphine analgesia in drug-treated and control rats.

To render rats tolerant to morphine analgesia, specially formulated pellets containing 75 mg of morphine base were implanted s.c. for 3 days, as described by Way *et al.* [14]. Control rats were implanted with a placebo pellet containing lactose instead of morphine.

The effects of acute treatment with AT on the intensity and duration of morphine analgesia in naive and morphine-tolerant rats were examined by plotting the reaction times on the hot plate against time (in minutes) after the administration of morphine. Amitriptyline (20 mg/kg) was always given i.p. 1 hr before the administration of morphine.

Tissue distribution of [^{14}C]morphine and its excretion in urine. Concentrations of total ^{14}C, [^{14}C]morphine and [^{14}C]MG in brain, plasma, liver, kidney, and urine were measured at 30, 60 and 90 min after the administration of [^{14}C]morphine to saline and AT-treated rats. Amitriptyline (20 mg/kg, i.p.) was given 1 hr prior to [^{14}C]morphine administration. Control rats received saline and the same dose of [^{14}C]morphine. After injection of [^{14}C]morphine, the rats were placed in individual metabolism cages (Maryland Plastics, New York, NY) for urine collection. To prevent urination while killing by decapitation, the rat was anesthetized with ether and its penis was clamped with an arterial clamp. All urine from the urinary bladder was collected and added to the previously excreted urine. The pH of urine was measured with pHydrion paper (Micro-Essential Lab, New York, NY) shortly after collection. Blood samples were collected in heparin-treated beakers after the animals were killed. Plasma was separated shortly after collecting the blood. The brain was removed (the surface was washed with saline, and blotted dry) and placed on dry ice. The entire brain, liver, kidney, plasma, and urine were kept frozen until analysis for concentrations of [^{14}C]morphine and [^{14}C]MG.

Analytical procedures and measurements of [^{14}C]morphine and [^{14}C]MG. For determination of ^{14}C concentrations in brain, liver, and kidney, the tissues were homogenized with distilled water at 1:4 (w/v) suspensions. The concentrations of total ^{14}C in the tissues were determined as described previously [10]. Concentrations of total ^{14}C in plasma and urine were determined by directly counting 0.3 ml of plasma or 0.05 ml of urine with 15 ml of ACS scintillation solution (Amersham Corp.) The concentrations of morphine and MG in tissue and urine were measured by a modified extraction method of Yeh and Woods [15], as described previously in detail [16].

Radioactivity was counted in a Packard Tri-Carb liquid scintillation counter, model 3330 (Packard Instrument Co., Inc., Downers Grove, IL). Counting efficiency and quenching correction were made by the internal method using [^{14}C]toluene as an internal standard.

A two-tailed Student's *t*-test was used to analyze the statistical significance of differences between treated and control groups.

RESULTS

Effects of AT on the analgesic effect and brain levels of morphine in naive rats. The time–response curves for morphine analgesia in rats receiving morphine alone and for those receiving AT plus morphine are shown in the left panel of Fig. 1. When the analgesic reaction time of the morphine control rats, measured at 60-min, was compared with that measured at 30-min, there was no significant difference. The analgesic reaction times of rats receiving AT plus morphine measured at 30 and 60 min were maximum. The analgesic reaction times of control and the AT + morphine-treated rats at 90 min however, were significantly shorter than their respective 30-min values.

Amitriptyline (20 mg/kg), administered 1 hr prior to morphine injection, caused an increase in the intensity and duration of the morphine analgesic response. Amitriptyline + morphine-treated rats achieved the maximum analgesic effect (no reaction time on the the hot plate within a 30-sec period), and it persisted from 30 to 60 min after the administration of morphine. Morphine control rats, which were given morphine alone, never demonstrated a maximum analgesic effect. Amitriptyline control rats receiving AT alone showed no analgesia. The analgesic reaction times of these rats remained within the range of the pre-drug control value (Fig. 1).

The concentrations of [^{14}C]morphine in the brains of control and AT-treated rats at different time intervals after the administration of [^{14}C]morphine are illustrated in the right panel of Fig. 1. As with analgesia, there was no significant difference between the brain concentrations of morphine at 60 and 30 min, in control or AT-treated rats. The brain concentrations of [^{14}C]morphine at the 90-min interval, however, were significantly lower than those found at 30 min in the control and AT-treated animals. These results clearly indicate that the morphine analgesia was directly related to brain concentration of morphine in the presence or absence of AT.

Since we had noted in a pilot experiment that AT

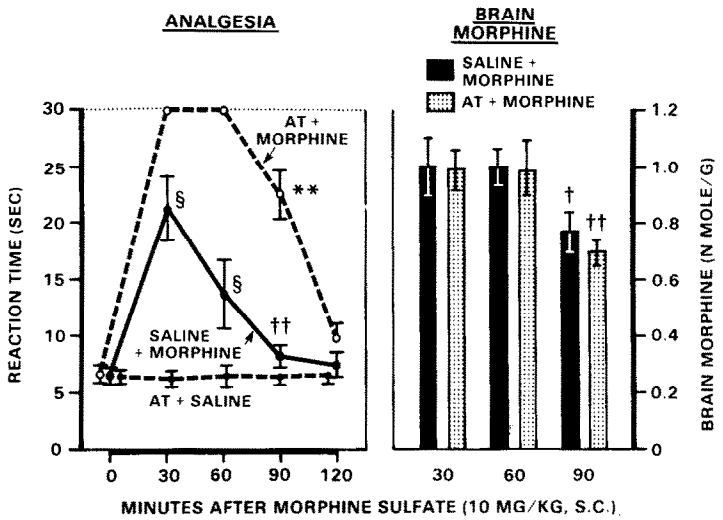

Fig. 1. Effects of amitriptyline (AT) treatment on the time–response curve of morphine analgesia (left panel) and brain concentrations of morphine (right panel) in naive rats. Rats (left panel) were given AT (20 mg/kg, i.p.) or saline 1 hr prior to administration of morphine (10 mg/kg, s.c.) or AT 1 hr prior to saline for measurement of analgesia. Three other groups of rats (right panel) were given the same doses of AT and [^{14}C]morphine (10 mg/kg, 20 μCi/kg, s.c.), and the animals were killed 30, 60 or 90 min after administration of [^{14}C]morphine. Each vertical bar is the mean ± S.E. from at least five rats. Key: ** denotes a value significantly different from the saline plus morphine group at $P < 0.01$; † denotes values significantly different from its respective 30-min values at $P < 0.05$; ‡ denotes a value significantly different from its respective 30-min value at $P < 0.01$; and § denotes a value significantly different from the AT plus saline group at $P < 0.01$.

treatment caused hypothermia, we questioned whether AT-induced hypothermia had caused the observed potentiation of morphine analgesia in AT-treated rats. For this reason, we investigated the effect of acute AT treatment on morphine analgesia in rats whose rectal temperatures were maintained at 37°. A similar potentiation of morphine analgesia was found in temperature-controlled animals shielded from AT-induced hypothermia. The analgesic reaction time of AT-treated rats was 22.5 ± 2.4 sec (mean ± S.E., $P < 0.01$, compared to 11.4 ± 1.6 sec in controls) 30 min after morphine,

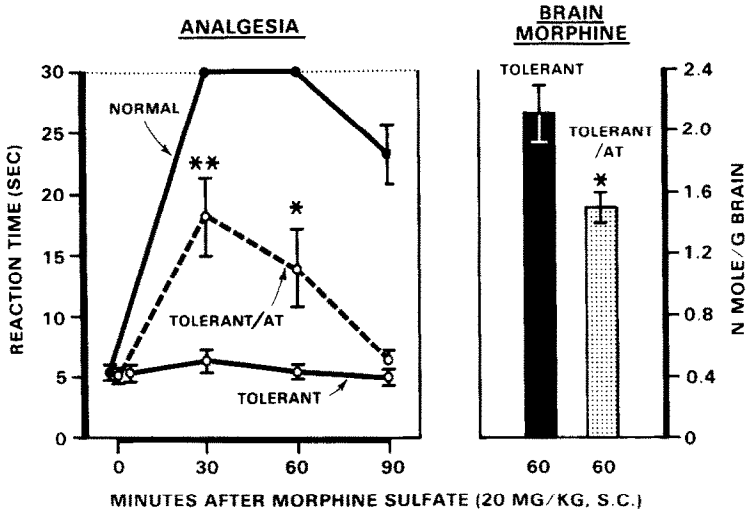

Fig. 2. Effects of amitryptyline (AT) treatment on the time–response curve of morphine analgesia (left panel) and on the brain concentration of morphine (right panel) in morphine-tolerant rats. Rats were rendered tolerant to morphine by s.c. implantation for 3 days of a pellet containing 75 mg of morphine base. Control rats were implanted with placebo pellets. Amitriptyline (20 mg/kg, i.p.) was administered 6 hr after removal of the pellet, and 1 hr later morphine (20 mg/kg, s.c.) was given for measurement of analgesia. Another group of morphine-tolerant rats was given the same dose of AT or saline and [^{14}C]morphine (20 mg/kg, 20 μCi/kg, s.c.), and the animals were killed 60 min after administration of [^{14}C]morphine. Each vertical bar is the mean ± S.E. from at least five rats. Key: (*) and (**) denote values significantly different from saline-treated morphine-tolerant rats at $P < 0.05$ and $P < 0.01$ respectively.

Table 1. Effect of amitriptyline (AT) on tissue distribution of [^{14}C]MG and total ^{14}C after administration of [^{14}C]morphine in naive rats*

Treatment	Liver		Kidney	Plasma
	Total ^{14}C†	[^{14}C]MG (as % of total ^{14}C)†	Total ^{14}C†	Total ^{14}C†
30 min				
Control	10.9 ± 0.40	83.3 ± 1.73	26.6 ± 2.41	9.96 ± 0.75
AT	13.6 ± 0.57‡	78.4 ± 1.81	41.4 ± 4.68‡	12.0 ± 0.84
60 min				
Control	8.56 ± 0.93	88.3 ± 1.68	31.2 ± 2.29	5.49 ± 0.38
AT	7.83 ± 0.46	85.2 ± 1.35	31.3 ± 1.87	5.74 ± 0.62
90 min				
Control	5.83 ± 0.31	87.0 ± 1.63	35.3 ± 4.47	5.21 ± 0.56
AT	6.66 ± 0.72	83.5 ± 1.19	77.9 ± 12.6§	6.19 ± 0.35

* Naive rats were injected with AT (20 mg/kg, i.p.) 1 hr before administration of [^{14}C]morphine (10 mg/kg, s.c.). The rats were killed 30, 60 or 90 min after administration of [^{14}C]morphine. Each value is the mean ± S.E. of five rats.

† Total ^{14}C is expressed as nmoles of total morphine equivalent per g of wet tissue. [^{14}C]MG is expressed as a percentage of total ^{14}C in the liver.

‡ Significantly different from control at $P < 0.05$.

§ Significantly different from control at $P < 0.01$.

and 13.6 ± 2.1 sec ($P < 0.05$, compared to 8.1 ± 0.8 sec in controls) 60 min after morphine.

Effects of AT on the analgesia and brain concentration of morphine in morphine-tolerant rats. Tolerance to morphine analgesia was evidenced by a marked reduction in analgesic reaction time after the administration of a challenging dose of morphine (left panel, Fig. 2). A challenging dose of morphine (20 mg/kg, s.c.), which produced a maximum analgesic response for more than 60 min in naive rats, failed to produce any analgesia in morphine-implanted rats. Figure 2 also indicates that the acute administration of AT partially restored the analgesia induced by 20 mg/kg of morphine in morphine-tolerant rats. AT, however, did not restore the full analgesic potency of morphine; its effect was somewhat intermediate between the analgesia seen in the naive and morphine-tolerant rats. As shown in the right panel of Fig. 2, the concentration of [^{14}C]morphine in the brains of AT-treated morphine-tolerant rats was significantly lower than that of saline-treated morphine-tolerant rats. This increase in analgesia with a corresponding lower brain concentration of [^{14}C]morphine indicates that the interaction between AT and morphine might be pharmacodynamic rather than pharmacokinetic.

Effects of AT on the tissue distribution and the urinary excretion of morphine and MG in naive and

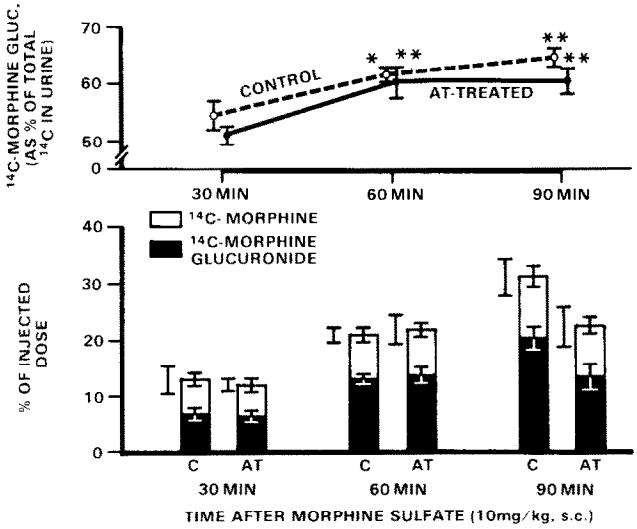

Fig. 3. Effects of amitriptyline (AT) treatment on urinary excretion of [^{14}C]morphine and [^{14}C]morphine glucuronide (bottom panel) and on the percentages of total ^{14}C in urine as [^{14}C]morphine glucuronide (top panel) after administration of [^{14}C]morphine in naive rats. Treatment of the rats is described in the legend of Fig. 1. Data were calculated for urine collected from cage and bladder at the time intervals indicated. Each value is the mean ± S.E. from at least five rats. The vertical lines outside the bars in the bottom panel are means ± S.E. of total ^{14}C in the urine. Key: (*) and (**) indicate significant differences from the 30-min value of each respective group at $P < 0.05$ and $P < 0.01$ respectively.

morphine-tolerant rats. The effects of acute AT treatment on tissue distribution of [^{14}C]MG and total ^{14}C after administration of [^{14}C]morphine in naive rats are presented in Table 1. The total ^{14}C in the kidneys of AT-treated rats was significantly higher than that of controls at 30 and 90 min after morphine. No significant difference in the total ^{14}C in the plasma of the two groups was found at any time interval studied.

The total ^{14}C in the liver measured 30 min after administration of [^{14}C]morphine was slightly higher in AT-treated rats than in control animals, with the difference being statistically significant. There were no significant differences, however, between the total ^{14}C in the livers of AT-treated and control groups at either 60 or 90 min after morphine. The percentage of total ^{14}C in the liver present as [^{14}C]MG was similar in AT-treated and control groups at all three time intervals. In addition, no change in the percentage of total ^{14}C in the liver as [^{14}C]MG was found with respect to time in either AT-treated or control groups. The values remained in the 78–87 per cent range throughout the course of the experiment.

Figure 3 illustrates the effects of acute treatment with AT on the urinary excretion of [^{14}C]morphine and [^{14}C]MG in naive rats. As shown in the bottom panel of Fig. 3, there were no significant differences between AT-treated and control rats in the urinary excretion of [^{14}C]morphine, [^{14}C]MG, or total ^{14}C at any of the time intervals studied. The percentage of total ^{14}C in the urine as [^{14}C]MG was also not significantly different between the AT-treated and control groups at any of the time intervals (top panel, Fig. 3). In both the control and AT-treated rats, however, the percentage of total ^{14}C in the urine as [^{14}C]MG was significantly increased with time after the administration of [^{14}C]morphine.

The effects of acute AT treatment on liver concentration and urinary excretion of [^{14}C]MG and total ^{14}C after administration of [^{14}C]morphine to morphine-tolerant rats are presented in Table 2. The amount of total ^{14}C in the liver or urine and the concentrations of [^{14}C]MG in the liver and urine, expressed either as the actual amounts or as percentages of total ^{14}C in the liver or urine, were not significantly different between AT-treated and control groups.

DISCUSSION

The studies described here have confirmed and extended our preliminary finding [17] that acute AT treatment increases the intensity and prolongs the duration of morphine-induced analgesia in naive and morphine-tolerant rats. A similar study, recently conducted by Malseed and Goldstein [18] using a cat tail-flick analgesic testing procedure, led to the same general conclusion. The potentiating effect of AT on morphine analgesia occurred with doses of AT that produced no obvious effects of their own under the experimental conditions used in the present studies. Whether tricyclic antidepressants themselves produce analgesia appears to be controversial, depending on the methods used to measure analgesia. Using rabbit dental pain as a measurement of analgesia, some investigators have reported that tricyclic antidepressants exert an analgesic effect [19]. Others, however, have reported that tricyclic antidepressants have no analgesic effect on mice, as measured by the hot plate method [20].

Determination of changes in brain concentrations of morphine may provide important information for elucidating whether the drug interaction between morphine and AT involves a dispositional change, alteration of the blood–brain barrier, or changes in CNS sensitivity to morphine. Way [21] reported that the pharmacological effects of morphine appear to correlate well with the concentration of morphine in the brain. Several other investigators have found that in rats there is a positive relationship between the concentration of morphine in the brain and the degree of analgesia [22, 23]. The results of the present study support this hypothesis and further demonstrate a positive relationship between brain concentration of morphine and analgesic response in the presence and absence of AT. Our results clearly indicate that the observed prolongation of morphine analgesia by AT treatment was not due to an increase in the brain concentration of morphine. However, since we (like most other investigators) measured whole brain concentration of morphine rather than the concentration of morphine in specific areas of

Table 2. Effects of amitriptyline (AT) on liver concentrations and urinary excretion of [^{14}C]MG and total ^{14}C after administration of [^{14}C]morphine to morphine-tolerant rats*

	Liver		Urine	
Treatment	[^{14}C]MG (nmoles/g)	Total ^{14}C (nmoles/g)	[^{14}C]MG (% of injected dose)	Total ^{14}C
Control	18.1 ± 0.82 (89.3 ± 0.51%)†	20.2 ± 1.01	11.3 ± 1.44 (63.9 ± 2.35%)	17.8 ± 2.39
AT	18.2 ± 1.45 (87.4 ± 0.94%)	20.8 ± 1.60	11.8 ± 1.10 (62.1 ± 1.67%)	19.1 ± 1.88

* Rats were made tolerant to morphine by s.c. implantation of morphine pellets for 3 days. Six hours after removal of the pellet, 50 per cent of the rats were injected with AT (20 mg/kg, i.p.), and the remaining 50 per cent were injected with saline, as controls. One hour after treatment with AT or saline, all of the rats were given [^{14}C]morphine (20 mg/kg, s.c.) and decapitated 1 hr later. Urine was collected from the cage and bladder. Each value is the mean ± S.E. of five rats.

† Numbers in parentheses are percentages of total ^{14}C in the liver or urine as [^{14}C]MG.

brain, the possibility that AT treatment might have produced slight increases in the morphine concentration of highly sensitive areas of the brain cannot be eliminated. Some investigators have demonstrated that certain areas such as the periaqueductal gray of the brain are highly sensitive in the production of narcotic analgesia [24, 25].

Since morphine is metabolised primarily to morphine glucuronide, which is analgesically inactive [26], many interactions between morphine and other compounds could be explained on the basis of the effect these compounds have on morphine biotransformation. For example, Yeh and Mitchell [27] suggested that acute pargyline treatment prolonged morphine analgesia by inhibiting morphine metabolism, based on the findings that pargyline treatment elevated the brain concentration of morphine and decreased the rate of morphine glucuronidation measured *in vitro*. Similarly, Sprague and Takemori [28] suggested that increased morphine analgesia produced by methamphetamine could be partially due to methamphetamine inhibition of morphine biotransformation. We recently developed a simple method that can facilitate the study of metabolic drug interactions with morphine [16]. In that study, we demonstrated that drugs such as SKF 525-A, which inhibited morphine biotransformation, caused a dose-related decrease in the percentages of total ^{14}C in the liver, plasma or urine as [^{14}C]MG 1 and 2 hr after the administration of [^{14}C]morphine. The fact that AT treatment did not change the percentage of total ^{14}C in liver or urine as [^{14}C]MG indicates that AT treatment exerted no significant effect on morphine metabolism *in vivo*. The finding that AT treatment had no significant effect on brain levels of morphine in naive rats is supporting evidence for this hypothesis. It is anticipated that inhibition of morphine biotransformation would result in a higher concentration of morphine in the brain, as demonstrated in our previous studies on the interaction of tricyclic antidepressants with pentobarbital [1] or methadone [11] and of SKF 525-A with morphine [16].

In addition to metabolism, other factors may affect the brain concentration of morphine. The brain uptake of morphine is directly proportional to the circulating blood levels of morphine which, in turn, are dependent upon the rate of absorption, distribution, metabolism, and excretion of the compound. The fact that AT treatment did not affect the plasma concentration of morphine, or the urinary excretion of morphine and MG, eliminates the possibility that AT treatment might have affected the absorption or excretion of morphine. These facts, coupled with the finding that AT treatment exerted no significant effect on morphine metabolism, as mentioned above, indicate that the observed prolongation of morphine analgesia by AT treatment could not have been due to a change in the pharmacokinetics of morphine.

Although the mechanism of narcotic analgesic action has not been established, numerous attempts have been made to connect the pharmacologic effects of morphine with the biogenic amines in the brain. Among the biogenic amines that have been thought to be involved in the effects of morphine are epinephrine, norepinephrine, acetylcholine, dopamine and serotonin [29–33]. A number of studies have provided evidence that changes in the brain levels of one or several neurotransmitters, or in the neurotransmitter receptors, may result in changes in morphine analgesia (see reviews in Refs. 34–36). On the other hand, the ability of tricyclic antidepressants to prevent the reuptake by brain tissues of central amines, particularly norepinephrine, serotonin and dopamine, has been invoked to explain the antidepressant action of these agents [37–39]. In addition, recent reports suggest a direct interaction of tricyclic antidepressants with central adrenergic [40], serotonergic [41], and muscarinic [42] receptors. A review of the above literature suggests that morphine and tricyclic antidepressants may interact similarly with central biogenic amines. This suggestion thus leads us to postulate that amitriptyline potentiates morphine analgesia by increasing CNS sensitivity to morphine directly or indirectly by means of alterations in catecholaminergic, serotonergic, dopaminergic and/or cholinergic systems at either pre-synaptic (uptake) or post-synaptic (receptor) sites of the CNS. A similar mechanism has been proposed by other investigators to explain the potentiation of morphine analgesia or heroin toxicity by other tricyclic antidepressants [7, 18, 43, 44]. The biochemical basis for this proposed mechanism, however, remains to be elucidated. Another possible mechanism of potentiation of morphine analgesia by amitriptyline may be a direct interaction of amitriptyline with opiate receptors. Some tricyclic antidepressants were shown recently to displace the specific binding of naloxone in a crude membrane preparation from rat brain [45].

In conclusion, the present studies demonstrate that acute AT treatment enhanced morphine analgesia in naive and morphine-tolerant rats. A tissue distribution study revealed no indication of changes in the metabolism, brain concentration, or excretion of morphine associated with AT treatment. It can be concluded that the effect of AT on morphine analgesia is a pharmacodynamic one, possibly mediated by an alteration of neurotransmitters at the receptor sites, resulting in increased CNS sensitivity to morphine analgesia.

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