ELSEVIER

Pharmacology, Biochemistry and Behavior 69 (2001) 419–424

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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On the mechanism of tolerance to morphine-induced Straub tail reaction in mice

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Received 22 January 1999; received in revised form 27 February 2001; accepted 7 March 2001

Abstract

The effect of 5-HT and opioid receptor antagonists on morphine-induced Straub tail was studied in mice. Straub tail behavior was induced by subcutaneous administration of different doses (20, 30, and 40 mg/kg) of morphine hydrochloride to mice. The effect of morphine was dose-dependent. Maximum response was obtained with 40 mg/kg of the drug. The response induced by morphine (20 and 40 mg/kg) was decreased by different doses of intraperitoneal injection of naloxone (1 and 2 mg/kg) or methysergide, mianserin, and ritanserin (1 and 2 mg/kg). The effect of morphine (40 mg/kg) was also reduced by intracerebroventricular injection of naloxone (0.4–0.8 μg/animal) or mianserin (2 and 4 μg/animal). Different groups of mice received one daily dose (50 mg/kg sc) of morphine sulfate for 3 days to develop tolerance to morphine. The Straub tail reaction induced by morphine hydrochloride (40 mg/kg) was tested on the fourth day. Naloxone injection (1 and 2 mg/kg ip) on Day 3 (1 h after morphine sulfate injection) or on Day 4 (1 h before test dose of morphine hydrochloride), decreased tolerance induced to morphine. Methysergide, mianserin, or ritanserin (intraperitoneal) on Days 2 and 3 (1 h after morphine sulfate injection) or on Day 4 (1 h before test dose of morphine hydrochloride), also decreased tolerance induced to morphine. Intracerebroventricular injection of either naloxone or mianserin also reduced tolerance to morphine. It is concluded that 5-HT_2 and opioid receptor mechanisms are involved in morphine-induced Straub tail reaction and tolerance induced to morphine also may be mediated through these receptors.

Keywords: Morphine; 5-HT receptors; Naloxone; Tolerance; Straub tail; Mice

1. Introduction

The opioids contract the sacrococcygeus muscle in mice, which results in erection of the tail (Straub tail reaction) (Bilbey et al., 1960; Narita et al., 1993). The morphine-induced Straub tail is a reflex phenomenon originating in the spinal cord in mice (Hasegawa et al., 1990). The response has been shown to be mediated through central μ_2 opioid receptor (Nath et al., 1994). The existence of 5-HT (Hamon et al., 1989) and opioid receptors (Slater and Patel, 1983) in the spinal cord has been reported.

Recent studies have shown that spinal serotonergic system contributes to spinal opiate-induced analgesia (Crisp et al., 1991). Morphine has been also shown to stimulate synthesis of 5-HT in different brain areas (Brase, 1979). The opioid may potentiate depleting effect of fenfluramine, suggested that opiates play a facilitatory role in striatal serotonin release (Parenti et al., 1983). The serotonergic system seems to be involved in morphine withdrawal jumping (Samanin et al., 1980) and quasi-morphine withdrawal (Neal and Sparber, 1990). Our previous study showed that 5-HT_2 receptor mechanism is involved in tolerance induced to morphine antinociception (Zarrindast et al., 1995). Straub tail reaction can be one of the main determinants in the testing of opioid activity in mice, and it may be essential to understand the mechanism(s) involved in the tolerance induced to this response. To examine the effects of 5-HT_2 and opioid receptor mechanisms in Straub tail reaction, we studied the effects of 5-HT_2 receptor antagonists and naloxone on morphine-induced Straub tail.

2. Methods and materials

2.1. Animals

Male albino mice (20–25 g) were used in these experiments. They were housed 10/cage, in colony room 12/12-h

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0091-3057/01/$ – see front matter
PII: S0091-3057(01)00519-6

light/dark cycle at 22±2°C. The animals had free access to food and tap water except during the time of experiments. Each animal was used once only and was euthanized immediately after experiments. The experimental protocol was approved by the Research and Ethics Committee of the School of Pharmacy, Tehran University of Medical Sciences (No. P-542/97).

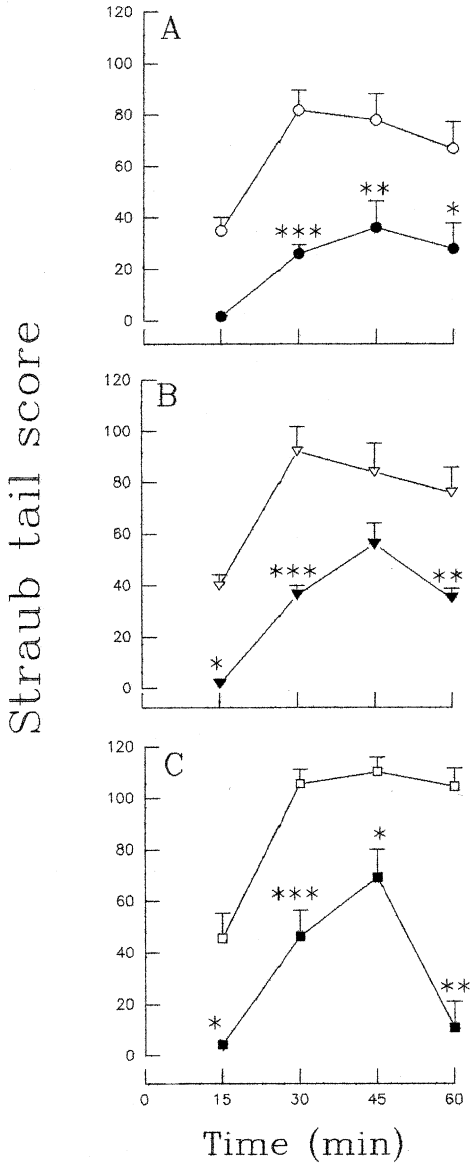

Fig. 1. Time course effect of morphine-induced Straub tail reaction in nontolerant and tolerant mice. Animals were injected subcutaneously either with saline (10 ml/kg; open symbols, nontolerant animals) or with morphine sulfate once daily for 3 days (50 mg/kg; solid symbols, tolerant animals), and they were tested on Day 4 with different test doses of morphine hydrochloride (A) 20, (B) 30, and (C) 40 mg/kg. Straub tail scores over the 15-min periods were recorded 15, 30, 45, and 60 min after morphine administration. Each bar is the mean±S.E.M. of nine animals. * $P<.05$; ** $P<.01$; *** $P<.001$, different from saline control group.

Table 1
Effects of 5-HT antagonists and naloxone on morphine-induced Straub tail in nontolerant mice

Treatment		Straub tail scores/30 min		
		Saline	Morphine 20	Morphine 40
Saline (ml/kg)	10	0.0±0.0	117.6±19.6	162.5±13.6
Naloxone (mg/kg)	1	0.0±0.0	1.4±0.6**	12.0±2.1**
	2	0.0±0.0	6.0±1.7**	11.5±3.9**
Methysergide (mg/kg)	1	0.0±0.0	74.9±9.1*	95.2±10.1**
	2	0.0±0.0	58.8±5.9**	80.4±10.2**
Mianserin (mg/kg)	1	0.0±0.0	109.4±9.6	69.1±3.6**
	2	0.0±0.0	35.7±5.9**	60.6±9.1**
Vehicle (ml/kg)	10	0.0±0.0	116.5±13.1	163.4±17.2
Ritanserin (mg/kg)	1	0.0±0.0	26.8±3.6**	61.5±5.3**
	2	0.0±0.0	30.7±3.5**	53.3±3.2**

Animals were treated intraperitoneally either with saline, vehicle (a drop of acetic acid+saline) or with different doses of 5-HT antagonists (1 and 2 mg/kg) 60 min before and naloxone (1 and 2 mg/kg) 5 min before morphine injection. Straub tail score was recorded for 30 min. Values given are mean (range) from seven animals.

* $P<.05$, different from morphine respective control groups.

** $P<.001$, different from morphine respective control groups.

2.2. Chronic guide cannula implantation

Stainless steel guide cannula (23 gauge) were stereotaxically (David Koft Instruments, USA) implanted under anesthesia with pentobarbital (60 mg/kg ip) 5–7 days before the experiments. The guide cannula were implanted in the left lateral ventricle at the following coordinates based on the method of Jiang et al. (1990) with a minor modification: 2 mm lateral and 0.9 mm caudal to bregma at the depth of 3 mm. The drugs were injected in a volume of 1 μl in a period of 2 min, by means of an internal cannula (30 gauge) connected by polyethylene tubing to a 10-μl Hamilton syringe and the injection cannula was left in place for a further 1 min before being slowly withdrawn.

2.3. Straub tail recording

Mice were placed individually in glass boxes (20×30 cm wide, 30 cm long) and allowed to habituate for 30 min before morphine injection. Immediately after the opioid administration, each animal was placed into the box and the response was recorded by direct observation. The subject's behavior was sampled each 15 s and the Straub tail response was graded as follows: 0=no response, 1=1–45°, 2=46–90°. At each 30-min period, the total accumulated scores over 30-min periods were used to assess the response. For time course effect of morphine (Fig. 1), total accumulated scores over each 15 min was recorded. The Straub tail score ±S.E.M. of at least seven mice was recorded.

2.4. Drugs

The following drugs were used: morphine sulfate and morphine hydrochloride (MacFarlan, Smith, England),

naloxone hydrochloride (Dupont, Germany), mianserin, and ritanserin (Research Biochemical, USA), methysergide (Sandoz, Switzerland). All drugs were dissolved in physiological saline except for ritanserin, which was dissolved in a drop of acetic acid and was diluted with physiological saline. The drugs' solution was prepared immediately before injection and were administered in volume of 10 ml/kg. Morphine sulfate was used to develop tolerance and morphine hydrochloride (test dose) was used to induce Straub tail reaction.

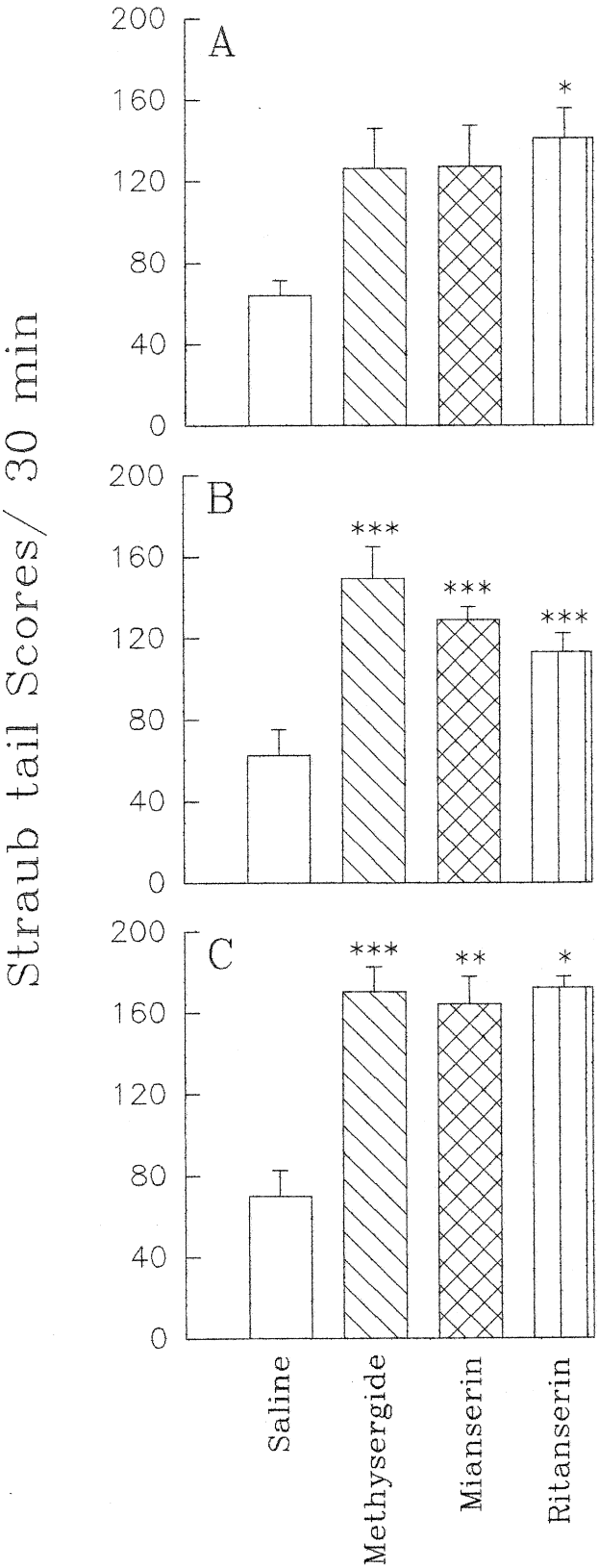

Table 2
Effects of naloxone and 5-HT receptor antagonists on morphine-induced Straub tail in tolerant mice

Pretreatment		Straub tail scores/30 min
Saline (ml/kg)	10	63.4 ± 8.1
Naloxone (mg/kg)	1	132.8 ± 12.9 *
	2	141.8 ± 17.0 **
Methysergide (mg/kg)	0.5	156.7 ± 12.5 **
	1	164.9 ± 7.3 **
Mianserin (mg/kg)	0.5	151.0 ± 14.2 **
	1	167.3 ± 11.3 **
Vehicle (ml/kg)	10	64.9 ± 7.8
Ritanserin (mg/kg)	0.5	124.2 ± 11.3 *
	1	139.2 ± 13.7 **

Mice were treated intraperitoneally either with saline, vehicle, or with different doses of naloxone or 5-HT receptor antagonists, 24 h prior to test dose of morphine hydrochloride (40 mg/kg; 1 h after morphine sulfate, during development of tolerance). Straub tail score was recorded for 30 min. Each point is mean ± S.E.M. of nine animals.

* $P < .01$, different from respective control groups.

** $P < .001$, different from respective control groups.

2.5. Statistical analysis

Analysis of variance (ANOVA) followed by Tukey's test was used to evaluate significance of the results obtained. Difference with $P < .05$ was considered significant.

3. Results

3.1. Tolerance to Straub tail induced by morphine in mice

Morphine-induced Straub tail reaction in tolerant and nontolerant mice has been shown in Fig. 1A, B, and C. Different groups of mice received one daily dose (50 mg/kg sc) of morphine sulfate for 3 days to develop tolerance to morphine. Effect of different test doses of morphine hydrochloride in tolerant and nontolerant animals were examined. Three-way ANOVA was used with tolerant/nontolerant (Factor 1) and test doses of morphine (Factor 2: 20, 30, and 40

Fig. 2. Effect of 5-HT receptor antagonists on morphine-induced Straub tail in tolerant mice. Saline (10 ml/kg), methysergide (2 mg/kg), mianserin (2 mg/kg), or ritanserin (2 mg/kg) were administered intraperitoneally on (A) Day 2, (B) Day 3 during development of tolerance (1 h after morphine sulfate injection), or (C) Day 4 (1 h before test dose of morphine hydrochloride). The response of test dose of morphine hydrochloride (40 mg/kg) was recorded on Day 4, for a period of 30 min. Each bar is the mean ± S.E.M. of nine animals. * $P < .05$; ** $P < .01$; *** $P < .001$, different from saline control group.

Table 3
Effect of intracerebroventricular administration of naloxone and mianserin on morphine-induced Straub tail reaction in tolerant and nontolerant animals

Pretreatment (μg/animal)		Straub tail scores/30 min			
				Tolerant	
		Saline	Nontolerant	Day 3	Day 4
Saline	10	0.0 ± 0.0	151.6 ± 10.9	74.6 ± 10	67.5 ± 10.3
Naloxone	0.4	0.0 ± 0.0	74.1 ± 8.2***	129.0 ± 9.0 *	132.8 ± 12.5 **
	0.8	0.0 ± 0.0	49.7 ± 3.1***	146.0 ± 10.3***	147.4 ± 14.4 **
Mianserin	2	0.0 ± 0.0	106.1 ± 14.1 *	108.7 ± 15.2	124.5 ± 10.8 *
	4	0.0 ± 0.0	76.3 ± 8.4***	135.3 ± 11.2 **	133.7 ± 15.3 **

Nontolerant mice were pretreated intracerebroventricularly either with saline, different doses of naloxone (0.4 and 0.8 μg/animal), or mianserin (2 and 4 μg/animal) 15 min before test dose of morphine hydrochloride (40 mg/kg sc). Tolerant animals were treated intracerebroventricular either with saline or with the same doses of naloxone and mianserin on Day 3 (1 h after subcutaneous injection of morphine sulfate during tolerance development) or on Day 4 (1 h prior to test dose of morphine hydrochloride). Straub tail score was recorded for 30 min. Each point is mean ± S.E.M. of seven animals.

* $P < .05$, different from morphine respective control groups.

** $P < .01$, different from morphine respective control groups.

*** $P < .001$, different from morphine respective control groups.

mg/kg sc) as fixed factors and time (Factor 3: 15, 30, 45, and 60 min) as repeated measure factors. Analysis indicates that the three-way interaction was not significant [$F(6,168) = 0.28$, $P > .05$]. There was a significant time by morphine test doses interaction [$F(6,168) = 2.8$, $P < .05$]. There was a significant time by tolerance interaction, i.e., in tolerant mice, the peak Straub tail score was observed in 45 min, but in the nontolerant mice, the peak effect was observed in 30 min [$F(3,168) = 4.6$, $P < .01$]. There was no significant interaction between tolerance and morphine test doses [$F(2,56) = 0.6$, $P > .05$]. The three main effects were significant [$F_{time}(3,168) = 109.7$, $P < .001$; $F_{morphine}(2,56) = 7.5$, $P < .01$; and $F_{tolerance}(1,56) = 76$, $P < .001$].

3.2. Effect of 5-HT receptor antagonists and naloxone on morphine-induced Straub tail reaction in nontolerant mice

Intraperitoneal pretreatment of animals with different doses of naloxone (1 and 2 mg/kg, 2 min) [$F(2,18) = 31.8$, $P < .0001$], methysergide (1 and 2 mg/kg, 60 min) [$F(2,18) = 5.5$, $P < .05$], mianserin (1 and 2 mg/kg, 60 min) [$F(2,18) = 11.9$, $P < .001$], or ritanserin (1 and 2 mg/kg, 60 min) [$F(2,18) = 39.2$, $P < .0001$] decreased Straub tail induced by test dose (20 mg/kg) of morphine hydrochloride. The same doses of naloxone [$F(2,18) = 111.1$, $P < .0001$], methysergide [$F(2,18) = 14.7$, $P < .001$], mianserin [$F(2,18) = 34.2$, $P < .0001$], or ritanserin [$F(2,18) = 33.8$, $P < .0001$] also decreased Straub tail induced by higher test dose (40 mg/kg) of morphine hydrochloride (Table 1).

3.3. Effects of 5-HT receptor antagonists and naloxone on morphine-induced Straub tail reaction in tolerant mice

Mice were administered one daily dose of morphine sulfate (50 mg/kg sc) for 3 days in order to develop tolerance, and Straub tail behavior induced by test dose of morphine hydrochloride was tested on the fourth day.

Administration of 2 mg/kg of methysergide, mianserin, or ritanserin on Day 2 [$F(3,32) = 3.6$, $P < .05$] (Fig. 2A) or on Day 3 [$F(3,32) = 18.2$ $P < .0001$] (Fig. 2B) 1 h after morphine sulfate during development of tolerance, or on Day 4 [$F(3,32) = 10.3$, $P < .0001$] (Fig. 2C) 1 h before the test dose of morphine hydrochloride (40 mg/kg) increased Straub tail reaction. Administration of naloxone (1 and 2 mg/kg ip) [$F(2,24) = 10.6$, $P < .001$], methysergide (0.5 and 1 mg/kg ip) [$F(2,24) = 34.7$, $P < .0001$], mianserin (0.5 and 1 mg/kg ip) [$F(2,24) = 23.7$, $P < .0001$] or ritanserin (0.5 and 1 mg/kg ip) [$F(2,24) = 12.3$, $P < .001$] on the third day (1 h after morphine sulfate) also showed a significant increase in Straub tail induced by test dose of morphine hydrochloride (40 mg/kg sc) in tolerant animals (Table 2).

Naloxone (1 and 2 mg/kg; 127.3 ± 9.2 and 133.1 ± 12.2, respectively) injection 1 h before administration of test dose of morphine hydrochloride (40 mg/kg sc) in tolerant mice also increased Straub tail reaction induced by morphine (63.9 ± 7.1) [$F(2,18) = 13.7$, $P < .001$].

3.4. Effects of intracerebroventricular administration of naloxone and mianserin on morphine-induced Straub tail reaction in tolerant and nontolerant mice

Intracerebroventricular pretreatment of animals with naloxone (0.4 and 0.8 μg/mice, 15 min) or mianserin (2 and 4 μg/mice, 15 min) [$F(4,30) = 16.4$, $P < .0001$] reduced Straub tail reaction induced by morphine hydrochloride (40 mg/kg sc) in nontolerant animals. However, intracerebroventricular administration of the same doses of naloxone or mianserin, on Day 3, 1 h after morphine sulfate administration [$F(4,30) = 5.9$, $P < .01$] and on Day 4, 1 h before test dose of morphine hydrochloride [$F(4,30) = 6.2$, $P < .001$] increased the morphine response in the tolerant mice (Table 3).

4. Discussion

In the present study, morphine-induced Straub tail reaction in mice dose dependently. The response induced by

morphine was decreased by either peripheral or central administration of naloxone, which may indicate that the response induced centrally and through opioid receptor mechanism. This is in agreement with previous studies shown by others indicating opioid receptor involvement in morphine-induced Straub tail behavior (Narita et al., 1993). The hypothesis can be also supported by the data indicating that morphine elicits analgesia through spinal and supraspinal mechanisms (Heyman et al., 1988; Paul et al., 1989), and that Straub tail behavior is induced through central μ_2 opioid receptors (Nath et al., 1994).

The present data showed that nonselective 5-HT receptor antagonist methysergide (Deakin and Green, 1978), which can block different 5-HT receptor subtypes, reduced morphine-induced Straub tail, therefore one may propose that 5-HT receptor mechanism is involved in the Straub tail reaction. This response has been shown by several authors previously (Adell et al., 1989; Dickinson and Curzon, 1983; Eison and Wright, 1992).

It is apparent that 5-HT receptors can be classified into at least three, possibly up to seven classes of receptors (for review, see Hoyer et al., 1994). They comprise the 5-HT_1, 5-HT_2, and 5-HT_3 classes, as well as the "uncloned" 5-HT_4 receptor. The 5-HT_5, 5-HT_6, and 5-HT_7 receptor genes have been cloned recently, but the receptors have yet to be fully characterised operationally and tranductionally in intact tissues, and as such their appellations must be considered provisional.

In the present work, intraperitoneal injection of 5-HT_2 receptor antagonists mianserin (Neal and Sparber, 1986) and ritanserin (Leysen et al., 1981) also reduced morphine-induced Straub tail. Therefore, at least 5-HT_2 receptors can be involved in the behavior. Present results obtained by peripheral administration may be supported by intracerebroventricular injection of mianserin and are consistent with the fact that 5-HT_2 receptors exist in brain (Hoyer et al., 1994). It has been shown that Straub tail response can be evoked by intrathecal injection of a agent that has both 5-HT_1 and 5-HT_2 agonistic properties but not selective 5-HT_2 receptor agonist indicating the possibility that both spinal 5-HT_1 receptors and central 5-HT_2 receptors may be involved in the response (Fone et al., 1989). Whether the response of 5-HT receptor antagonists is mediated through α_2-adrenoceptor blocking action should be examined.

Chronic administration of morphine produces tolerance to its analgesic, hyperthermic, hypothermic, respiratory depressant, euphoric, cataleptic, locomotor depressant, and stimulant actions (Bhargava, 1994). It would be interesting to see if tolerance can be developed to morphine-induced Straub tail reaction. The opioid and 5-HT_2 receptor mechanisms involved in the tolerance to morphine-induced Straub tail response was investigated in the present study. The opioid receptor antagonist naloxone or the 5-HT receptor antagonists methysergide, mianserin, or ritanserin were used to study expression and development of tolerance to Straub tail induced by morphine.

Present data indicate that daily administration of morphine sulfate (50 mg/kg sc) for 3 days developed tolerance to morphine-induced Straub tail. Tolerance to morphine analgesia was developed with a such procedure employed before (Zarrindast et al., 1997). The tolerance to morphine-induced Straub tail reaction was decreased when animals were administered (intracerebroventricularly or intraperitoneally) the opioid receptor antagonist naloxone on Day 3, during development of tolerance (third day of morphine sulfate injection), indicating that central opioid receptor mechanism(s) may be involved in the development of tolerance to morphine-induced Straub tail behavior. This is in agreement with data obtained by others in rats (Mushlin and Cochin, 1976). Our data also indicate that naloxone, when given 1 h before Straub tail testing (on Day 4), enhanced the Straub tail effect. The response of naloxone appeared to be dose-dependent. Such an effect was also observed whether the naloxone was administered intraperitoneally or intracerebroventricularly. Increase in the Straub tail scores by naloxone may be due to precipitation of withdrawal in the tolerant/dependent animals. However, μ opioid receptor involvement in tolerance to morphine-induced Straub tail reaction seems likely, the mechanism involved is not clear. It has been shown that μ opioid receptors down-regulated in the brain of morphine-tolerant and -dependent rats (Bhargava and Gulati, 1990). However, in mice and rats, others have shown that μ opioid receptors are up-regulated (Abdelhamid and Takemori, 1991; Rothman et al., 1991). Whether the change in number of opioid receptors is involved should be investigated.

Chronic administration of morphine to mice has been shown to be associated with increased turnover of 5-HT in the brain (Way et al., 1968) Furthermore, inhibition of 5-HT synthesis inhibited the development of tolerance and physical dependence on morphine in mice (Ho et al., 1972, 1973), and concurrent injection of tryptophan, a precursor for the synthesis of 5-HT, enhanced tolerance and physical dependence development (Ho et al., 1975). Other investigators, however, have not been able to confirm these findings (Cheney and Goldstein, 1971; Marshall and Grahame-Smith, 1971). It has also been suggested that tolerance to morphine is associated with up-regulation of 5-HT_2 receptors of certain brain regions (Gulati and Bhargava, 1988, 1989). Our results show that peripheral administration of 5-HT receptor antagonists, methysergide, mianserin, or ritanserin when employed during development of tolerance decreased development of tolerance to morphine-induced Straub tail reaction. The same results were obtained by intracerebroventricular injection of mianserin. Thus, the 5-HT receptor antagonists may prevent up-regulation of 5-HT receptors due to morphine administration and prevent tolerance to the opioid effect. The similar peripheral administration of the 5-HT receptor antagonists 1 h before administration of test doses of morphine (on Day 4) decreased the expression of tolerance to morphine-induced Straub tail reaction. Intracerebroventricular injection also

induced the same results. The data obtained by the 5-HT receptor antagonists are similar to those obtained by naloxone administration and possibly blockade influence of 5-HT receptors, which have been up-regulated (Gulati and Bhargava, 1988, 1989) during chronic morphine administration. The results may indicate that central 5-HT_2 receptor mechanism along with the opioid receptor mechanism are involved in the induction of tolerance to Straub tail behavior induced by morphine.

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