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Abstract

Previous investigations had shown that inhibitor of serotoinin reuptake transporter could attenuate morphine withdrawal syndrome in adult animals. In the present study, we determined whether that enhance serotonin-mediated neurotransmission by serotonin reuptake inhibitors is able to attenuate the expression of the naloxone-precipitated morphine withdrawal syndrome in neonatal Sprauge-Dawley rat born to dams rat received morphine injection since a week before mating till 5 days after delivery. Withdrawal syndrome of morphine, manifested as frequent abdominal stretching and yawning, was generated by injection of naloxone on postnatal day 5. Pre-injection with SRET inhibitors, fluoxetine, clomipramine or citolopram, significantly attenuated the naloxone-precipitated syndrome in a dose-dependent manner without apparent side effect. The rank order of inhibitory potency is citalopram= clomipramine > fluoxetine. This result suggests that inhibitor of SERT may be of potential in treating neonatal morphine withdrawal syndrome.

Key words: morphine withdrawal syndrome, neonatal rat, SERT inhibitor, naloxone

Serotonin reuptake inhibitors attenuating morphine withdrawal syndrome in neonatal rate passively exposed to morphine

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1. Introduction

Infant born to mothers addicted to morphine or heroin during pregnancy have great chance to produce acute withdrawal syndrome after birth. The withdrawal symptoms include jitteriness, irritability, shrill crying, hyperactivity-hypertonicity, poor feeding, vomiting, diarrhea, sneezing, tachypnea, and seizure (Volpe, 1995). Most of the newborns presenting apparent features of withdrawal syndrome require intensive care. In addition to supportive therapy to stabilize the vital sign, drug therapy with paregoric, phenobarbital, chlorpromazine or diazepam is frequently used to minimize the symptoms of central nervous and gastrointestinal systems. However, the side effects of these applied medication in CNS required careful monitoring. Thus, to improve the treatment outcome for neonatal morphine withdrawal syndrome development of new effective and safety medication is still needed

Serotonin (5-hydroxytyramine, 5-HT), an important biogenic amine, exerts its neurotransmission via activating different 5-HT subtype receptors in the CNS. Serotonin is synthesized from tryptophan through the action of tryptophan hydroxylase, and is released by prenaptic stimulation. Its action is terminated by uptaking through presynaptic serotonin reuptake transporter (SERT), which is a transmembrane protein uptaking serotonin by a sodium-dependent mechanism. Serotonin once been uptaked will be reused or degraded into hyrodroxyindoleactic acid (5-HIAA). Serotonin-mediated neurotransmission has long been implicated in the regulation of wide variety of cortical functions including modulation of appetite, memory, mood, emotionality, thermoregulation, and sexual behavior (Jacobs and Azmitia, 1992). The forebrain and spinal serotonin pathway are known to be involved in pain inhibition and morphine analgesia (Brase, 1979). It has been shown that deficiency in serotonin-mediated neurotransmission contributes to the expression of major depression and chronic pain (Archer et al., 1986), and therefore, selective SERT inhibitor such as citalopram, fluoxetine, and paroxetine are widely used in the treatment of depression, anxiety disorder, eating disorder, obsessive-compulsive disorder and substance abuse (Murphy, 1990; Singh et al., 2001). Previous reports had shown that acute administration of morphine could enhance brain serotonin synthesis, release and turn over rate in adult animals (Boadle-Biber et al., 1987; Tao and Auerbach, 1994). On the contrary, withdrawal to long-term exposure to morphine profoundly depressed serotonin level in many regions in CNS (Tao et al., 1998). Thus, withdrawal-induced reduction in brain serotonin level might be responsible for somatic as well as subjective symptoms of morphine withdraw. This idea is supported by the finding that administrating SERT inhibitor significantly attenuated the naloxone-precipitated hyperactivity of noradrenergic locus coeruleus (LC) neurons, an important brain substrate of opiate withdrawal, and the behavior changes (Akaoka and Aston-Jones, 1993; el-Kadi and Sharif, 1995; Harris and Aston-Jones, 2001; Lu et al., 2001; Rafieian-Kopaei et al., 1995). However, all these studies were performed in adult animals, yet no similar investigation is applied on the neonatal withdrawal syndrome. Thus, in the present study we determined whether naloxone-precipitated withdrawal syndrome in 5 day old rats could be attenuated by three different SERT inhibitors, fluoxetine, clomopiramine and citolopram.

2. Methods and Materials:

2.1 Chemicals

Morphine was purchased from the Narcotics Bureau of the National Health Adminstration, Taipei, Taiwan. Naloxone, fluoxetine, clomipramine, and citalopram were purchased from Tocris Cookson Ltd (U.K).

2.2 Animals.

Female Sprauge-Dawley rats (200 gm- 250 gm, purchased from National Experimental Animal Center, Taipei, Taiwan) were housed individually in plexiglass cages on a 12-hour light-dark cycle in Animal Center of Taipei Medical University. The room temperature was maintained at 24°C. Food and water were available *ad libitum* throughout the experiment.

2.3 Animal model of prenatal- and post-natal exposure to morphine

Adult female rats received bi-daily subcutaneous injection of morphine (2 mg/kg) for seven days before mating. After conception, the dosage of morphine was increased by 1 mg/kg per week. After delivery of the newborn rats, the dosage of morphine was increased by 1 mg/kg till the offspring were 5 day old when they were used for experiment. Control dam rats received bi-daily injection of normal saline. Rats born to morphine-treated dam rats are denoted as the morphine group rats, and rats born to saline-treated dam rats are denoted as the control group rats.

2.4 Naloxone-induced behavioral changes in the neonatal rats

To precipitate the withdrawal syndrome in the neonatal rats, we subcutaneously injected 1 mg/kg of naloxone, a non-selective opioid receptor antagonist, into the morphine group rats on PND 5. We, then, quantified the frequency and latency of abdominal stretching and yawning during a 2-hour observation period as the index for the severity of morphine withdrawal syndrome.

2.5 Postnatal treatment of fluoxetin(Flu)e, citolopram(Cit) and clopromarine(Clm) on the neonatal rats

Morphine group rats will receive subcutaneous injection of Flu (10 mg/kg, 20 mg/kg, or 40 mg/kg), Cit (2 mg/kg, 5 mg/kg, or 10mg/kg) or Clm (2 mg/kg, 5 mg/kg, or 10 mg/kg) 30 minutes before injection of naloxone.

2.6 Statistic analysis

Ratios of rats presenting naloxone-precipitated abdominal stretching and Yawning were analyzed using Chi-square test. For other data, one way ANOVA with post hoc Newman-Keuls test was used

Result

3.1 The effect of fluoxetine, clomipramine and citalopram on the expression of naloxone-precipitated abdominal stretching

All the morphine group rats presented frequent abdominal stretching after injection with naloxone. On the contrary, none of the control rats had abdominal stretching after injection with naloxone. Pre-injection with one of SERT inhibitors reducing the ratio of rat presented abdominal stretching in a dose-dependent manner (Fig.1A). The EC_{50} for flueoxitine, clomipramine, and citalopram in inhibiting naloxone-precipitating abdominal stretching is roughly between 20-40 mg/kg, 5-10 mg/kg, and 5-10 mg/kg, respectively. In addition, the SERT inhibitors also significantly prolonged the latency and decreased the frequency of abdominal stretching in the morphine group rats (Fig 1B ,C).

3.2 The effect of fluoxetine, clomipramine and citalopram on the expression of naloxone-precipitated yawning

Similar to that of abdominal stretching, all the morphine group rats presented yawning, and none of the control rats had yawning after injection with naloxone. Obviously, all three SERT inhibitors are more effective in attenuating the presentation of yawning than in attenuating abdominal stretching since only 20 mg/kg fluoxetine could reduce the ratio of rats presenting yawning to only 23% and 40 mg/kg fluoxetine could reduce to only 7% (Fig 2). On the other hand, 2 mg/kg of clomipramine or citalopram could complete abolish the symptoms of yawning.

Discussion

The present study demonstrated that inhibitor of SERT could effectively abolished the morphine withdrawal syndrome elicited by naloxone on the neonatal rats chronically and passively exposed to morphine. The major morphine withdrawal syndromes measured in this study are abdominal stretching and yawn. Although both symptoms have been documented in adult rats (Chen et al., 2003; Ramabadran, 1983), the expression of yawning is not reported in the neonatal rats including our previous report (Tao et al., 2001; Yeh et al., 2002). The reason for the lack of this presentation in our previous study is not clear. Nevertheless, yawning is one of apparent symptom of morphine or heroin withdrawal found in human including newborn baby (Bickel et al., 1988; O'Brien, 1996; Ostrea et al., 1975).

There are two reasons for choosing the three SERT inhibitors in this study. The first is that they are all highly potent in inhibiting SERT, and are at least 100 fold less potent in inhibiting nor-epinephrine reuptake transporter (NET) or dopamine reuptake transporter (DAT). According to the ligand binding analysis, the potency for these three compounds to binding to SERT is proximally 0.75 nM for citalopram, 0.5 nM for clomiprmaine and 2 nM for fluoxetine, and their potency for binding to norepinephrine reuptake transporter is roughly 3000 nM for citalopram, 100-200 nM for clomipramine, and 500 nM for fluoxetine (Millan et al., 2001; Owens et al., 1997). Their inhibitory potencies on DAT are far less than that in inhibiting NET. The second is that they are all commonly used in clinics, mainly used for anti-depressant, and their safety and side effect have been well-documented.

The rank order of the potency for the three SERT inhibitors in attenuating abdominal stretching or yawning is seems to be citalopram¡ clomipramine >fluoxetine, and the relative

ratio of EC_{50} in attenuating abdominal stretching between citalopram, clomipramine, and fluoxetine is roughly 1:1: 4 (5-10 mg/kg for citalopram, 5-10 mg/kg for clomipramine, 20-40 mg/kg for fluoxetine). This rank order and relative potency ratio is rather close to their potency in inhibiting SERT when measured by ligand binding analysis, which is 1:0.7: 2.8 as according to ligand binding analysis (0.75 nM for citalopram, 0.5 nM for clomiprmaine and 2 nM for fluoxetine) (Millan et al., 2001; Owens et al., 1997). Apparently, it is not consistent to that in inhibiting the NET, suggesting that the inhibitory effect of these three compounds in naloxone-precipitated withdrawal syndrome is likely through their inhibition on SERT. Previous reports had proved that serotonin system is one of the earliest neurotransmission system to be formed in the CNS (Lauder et al., 1982). At birth, this system is well formed both in structure and function and serotonin system contributes to the development of brain, especially for the cortex, in the early life (Pranzatelli, 1994; Pranzatelli and Martens, 1992). More importantly, the existence of SERT in the neonatal brain has been clearly demonstrated(McGrath et al., 1997), and application of SERT inhibitor, like clomipramine did altered the function of the serotonin-mediated neurotransmission (Hansen and Mikkelsen, 1998; Foguet et al., 1993). These reports further support our notion that these SERT inhibitors could act at SERT in neonatal rat brain.

It appears that the potent of all the examined SERT inhibitors in attenuating naloxone-precipitated yawning behavior are significant higher than that in abdominal stretching behavior. 20 mg/kg of fluoxetine could reduced the percentage of population presenting yawning to 23% but only reduced percentage of population presenting abdominal stretching to 84.6 %. On the other hand, 2 mg/kg of clompipramine or citalopram could completely abolish the yawning behaviors, but 10 mg/kg are required to abolish abdominal stretching. Such different sensitivity to SERT inhibitor suggests that the difference in underlying pathological mechanisms for these two different withdrawal symptoms. Previous report had indicated a complexity of neural systems in generating and modifying yawning behaviors (Argiolas and Melis, 1998). In brief, generation of yawning behavior includes activation of dopamine receptor, oxytocin receptor and glutamate receptor. On the contrary, activation of opioid receptor or serotonin receptor subtype, $5\text{-}HT_{1A}$ receptor or $5\text{-}HT_2$ receptor, serves as an inhibitory mechanism for yawn response. It is likely that theses neurophysiological properties render the sensitivity of SERT inhibitors to attenuate naloxone-precipitated yawning behavior by enhancing serotonin-mediated neurotransmission. However, the neural pathway for abdominal stretching is not known at present. We suspect that the ole of serotonin receptor in abdominal stretching might be not as essential as that in yawning behavior.

The result of this study is quite consistent with the study of SERT inhibitor on morphine withdrawal syndrome of adult rats (el-Kadi and Sharif, 1995; Lu et al., 2001; Rafieian-Kopaei et al., 1995), suggesting that either a deficiency in the serotonin-mediated neurotransmission contribute to the expression of morphine withdrawal syndrome both in adult and neonatal rats, or an increase in serotonin function by the action of SERT inhibitor counteracts the mechanisms responsible for the expression of morphine withdrawal syndrome. However, taking into account

the finding that NMDA receptor antagonists, like MK-801 or dextromethorphan, are as effective as SERT inhibitor in attenuating morphine withdrawal syndrome in both adult and neonatal rats (Tanganelli et al., 1991; Tiseo et al., 1994; Tokuyama et al., 1996; Trujillo and Akil, 1991; Yeh et al., 2002), it seems both glutamate and serotonin neurotransmitter systems are functionally converging in the neural network in generation of the withdrawal syndrome. It might be that the functions of these two systems are altered in opposite way during abstinence state, in which the function of NMDA receptor system is increased and the function of serotonin system is decrease. Alternatively, the functions of both systems might be not changed at all in abstinence state. Rather activation of NMDA receptor is required for the expression of withdrawal syndrome, and enhanced serotonin system in some way could counteract directly or indirectly with it. Both hypotheses all support the effectiveness of NMDA receptor antagonist and SERT inhibitor in attenuating morphine withdrawal syndrome.

In summary, the present study support the notion that SERT inhibitors is of potential in treating the acute morphine withdrawal syndrome in newborn baby. However, the pharmacokinetics, pharmacodynamics, as well as the drug safety of SERT inhibitors in newborn stage require carefully evaluation before any clinical application.

Acknowledge

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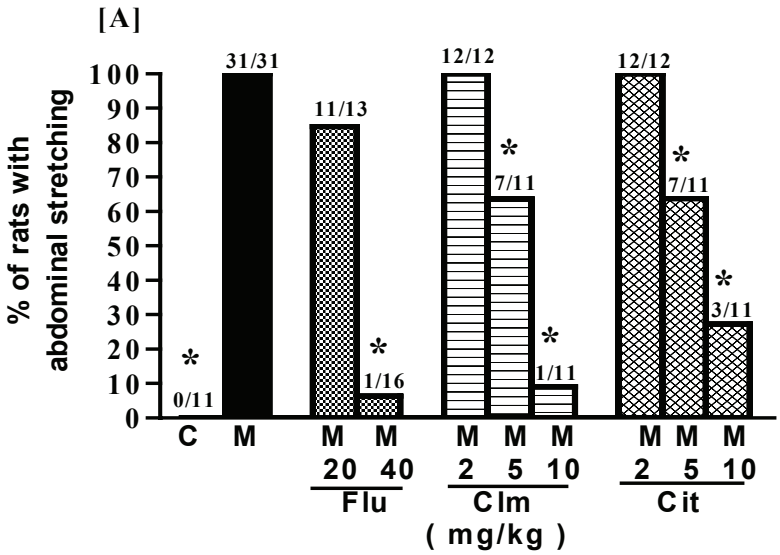
[A]
% of rats with abdominal stretching
100
90
80
70
60
50
40
30
20
10
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31/31
11/13
1/16
12/12
7/11
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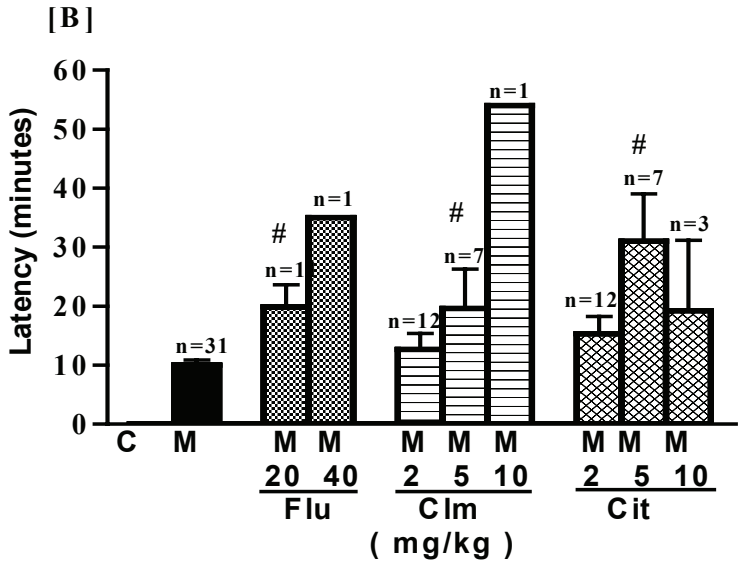
Flu Clm Cit
(mg/kg)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Latency (minutes)
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Flu Clm Cit
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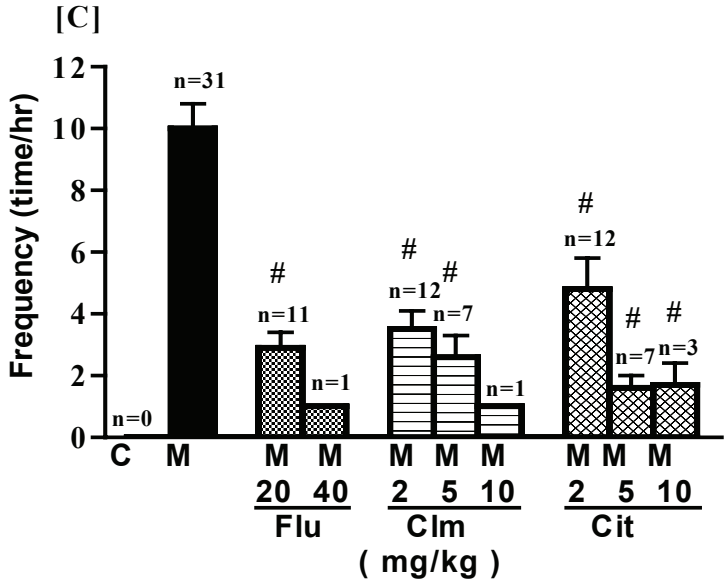
[C]
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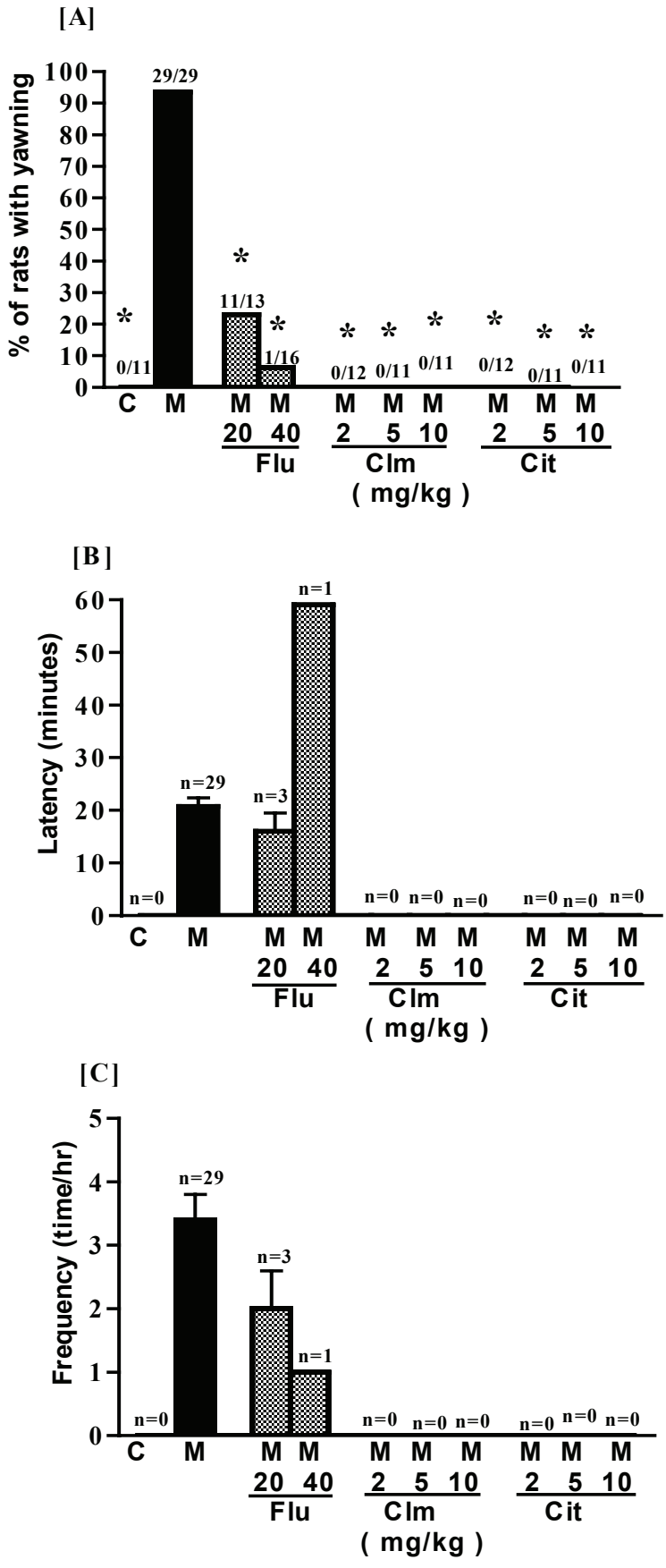
Flu Clm Cit
(mg/kg)


[A]
% of rats with yawning
100
90
80
70
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30
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29/29
11/13
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0/11
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0/11
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Cit
(mg/kg)
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Latency (minutes)
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Cit
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M 10
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M 2
M 5
M 10
Cit
(mg/kg)

Figure Legends

Figure 1. The effect of fluoxetine (Flu), clomipramine (Clm) and citalopram (Cit) on the naloxone-precipitated abdominal; stretching of control (C) and morphine (M) group rats. Data are mean ± S.E. [A]Percentage of rats presenting abdominal stretching in response to naloxone injection (1 mg/kg s.c.). The responding ratio of each experimental group is listed on the top pf each bar. [B]Latency to the first abdominal stretching. The number of rats showing abdominal stretching (n) are listed on the top of each bar. Statistic analysis was not able to performed when the number is lower than 3. A similar condition also occurred when comparing the frequency of abdominal stretching in [C].

* mean significantly different from that of morphine group rats (M) ($p< 0.05$, Chi-square test).

mean significantly different from that of morphine group rats (M) ($P <0.05$, one-way ANOVA with Newman-Keuls test)

Figure 2. The effect of fluoxetine (Flu), clomipramine (Clm) and citalopram (Cit) on the naloxone-precipitated yawning of control (C) and morphine (M) group rats. Data are mean ± S.E. [A]Percentage of rats presenting yawning in response to naloxone injection (1 mg/kg s.c.). The responding ratio of each experimental group is listed on the top pf each bar. [B]Latency to the first yawning. The number of rats showing yawning (n) are listed on the top of each bar. Statistic analysis was not able to performed when the number is lower than 3. A similar condition also occurred when comparing the frequency of yawning in [C].

* mean significantly different from that of morphine group rats (M) ($p< 0.05$, Chi-square test).

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