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Serotonin reuptake inhibitors attenuate morphine withdrawal syndrome in neonatal rats passively exposed to morphine

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Abstract

Previous investigations had shown that inhibitor of serotonin reuptake transporter (SERT) could attenuate morphine withdrawal syndrome in adult animals. In the present study, we determined whether postnatal injection of serotonin reuptake inhibitors, fluoxetine, clomipramine, or citalopram, is able to attenuate the expression of the naloxone-precipitated morphine withdrawal syndrome in 5-day-old neonatal Sprauge–Dawley rats born to dams rat that 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 fluoxetine, clomipramine, or citalopram, 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.

Keywords: Morphine withdrawal syndrome; Neonatal rat; Serotonin reuptake transporter inhibitor; Naloxone

1. Introduction

Infants 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, yawning, 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 the central nervous and gastrointestinal systems. However, the side effects of these applied medications in central nervous system (CNS) require 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 pre-synaptic stimulation. Its action is terminated by uptaking through pre-synaptic serotonin reuptake transporter (SERT), which is a transmembrane protein uptaking serotonin by a sodium-

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dependent mechanism. Serotonin once been uptaked will be reused or degraded into hyrodroxyindoleactic acid. Serotonin-mediated neurotransmission has long been implicated in the regulation of a 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 pathways 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, clomipramine, or fluoxetine, 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 from 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 that administrating SERT inhibitor significantly attenuated the naloxone-precipitated hyperactivity of noradrenergic locus coeruleus 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. Therefore, in the present study, we determined whether SERT inhibitors, fluoxetine, clomipramine, and citalopram, could attenuate naloxone-precipitated withdrawal syndrome in 5-day-old rats, which had passively exposed to morphine during the whole course of pregnancy.

2. Methods and materials

2.1. Chemicals

Morphine was purchased from the Narcotics Bureau of the National Health Administration, Taipei, Taiwan. Naloxone was purchased from Sigma/RBI (Natick, MA). Fluoxetine, clomipramine, and citalopram were purchased from Tocris Cookson (U.K).

2.2. Animals

Female Sprauge–Dawley rats (200 g–250 g, purchased from National Experimental Animal Center, Taipei, Taiwan) were housed individually in plexiglass cages on a 12-h 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. The animal study followed the guideline of the Animal Center of Taipei Medical University.

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 7 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 postnatal day 5. We, then, quantified the frequency and latency of abdominal stretching and yawning during a 2-h observation period as the index for the severity of morphine withdrawal syndrome.

2.5. Postnatal treatment of fluoxetine, citalopram, and clomipramine on the neonatal rats

Morphine group rats will receive subcutaneous injection of fluoxetine (20 mg/kg or 40 mg/kg), clomipramine (2 mg/kg, 5 mg/kg, or 10 mg/kg), or citalopram (2 mg/kg, 5 mg/kg, or 10 mg/kg) 30 min 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 analysis of variance (ANOVA) with post hoc Newman–Keuls test was used.

3. 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. Pre-

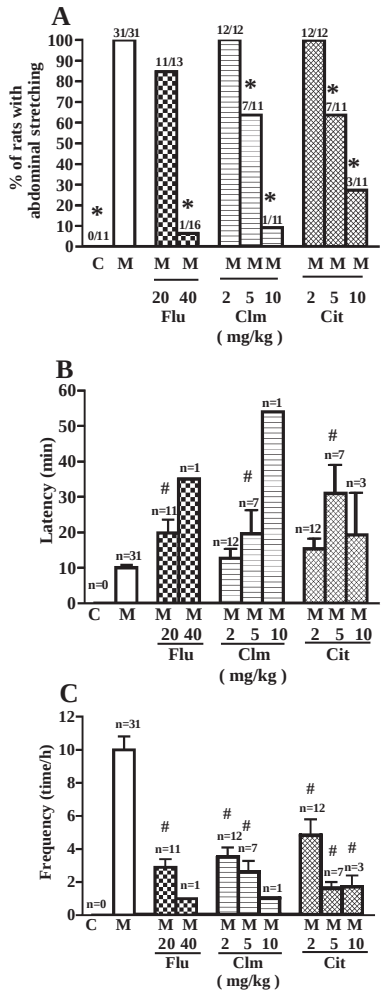

Fig. 1. The effect of fluoxetine (Flu), clomipramine (Clm), and citalopram (Cit) on the naloxone-precipitated abdominal stretching of control (C) and morphine (M) group rats. Data are mean±S.E.M. (A) Percentage of rats presenting abdominal stretching in response to naloxone injection (1 mg/kg s.c.).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

injection with one of SERT inhibitors dose-dependently reduced the percentage of morphine group rats presenting naloxone-precipitated abdominal stretching (Fig. 1A). The EC_{50} for fluoxetine, clomipramine, and citalopram in inhibiting 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). Furthermore, no apparent behavior change or mortality was induced by the injection of fluoxetine, clomipramine, or citalopram on the control or morphine group rats (data not shown).

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 20 mg/kg fluoxetine could reduce the percentage of morphine group rats presenting yawning to only 23%, and 40 mg/kg fluoxetine could reduce to 7% (Fig. 2). On the other hand, 2 mg/kg of clomipramine or

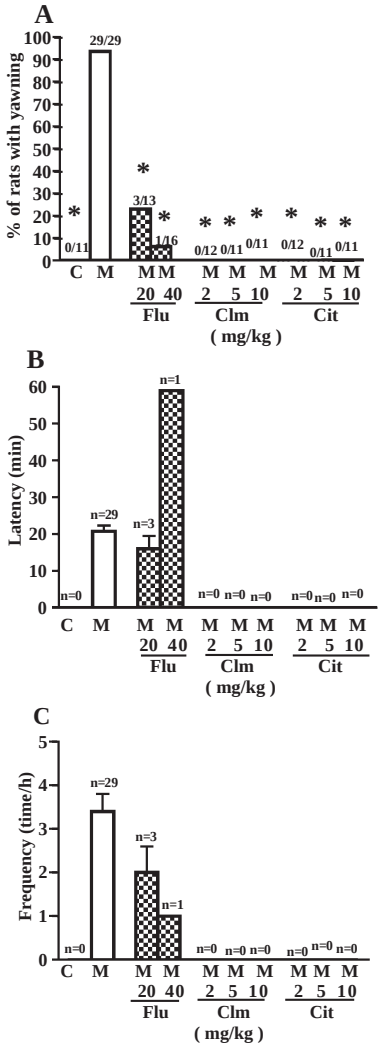

Fig. 2. The effect of fluoxetine (Flu), clomipramine (Clm), and citalopram (Cit) on the naloxone-precipitated yawning of control (C) and morphine (M) group rats. Data are mean±S.E.M. (A) Percentage of rats presenting yawning in response to naloxone injection (1 mg/kg s.c.). The responding ratio of each experimental group is listed on the top of each bar. (B) Latency to the first yawning. The number of rats showing yawning (n) is listed on the top of each bar. Statistic analysis was not able to be performed when the number is lower than 3. A similar condition also occurred when comparing the frequency of yawning in panel C. *Mean significantly different from that of morphine group rats (M) ($P<0.05$, Chi-square test).

citalopram could completely abolish the symptoms of yawning.

4. 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. We previously had used the same animal model to demonstrate the effectiveness of *N*-methyl-D-aspartate (NMDA) receptor antagonist, MK-801, and dextromethorphan, in attenuating neonatal morphine withdrawal syndrome (Yeh et al., 2002). The major morphine withdrawal syndromes measured in this study are abdominal stretching and yawning. 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 reason is that they are all highly potent and selective in inhibiting SERT. According to the ligand binding analysis, their potencies in inhibiting SERT are at least 100-fold higher than their potencies in inhibiting norepinephrine reuptake transporter (NET) or dopamine reuptake transporter (DAT). Accordingly, the affinities for these three compounds on SERT are proximally 0.75 nM for citalopram, 0.5 nM for clomipramine, and 2 nM for fluoxetine, and the affinities on NET are roughly 3000 nM for citalopram, 100–200 nM for clomipramine, and 500 nM for fluoxetine (Millan et al., 2001; Owens et al., 1997). On the other hand, their affinities on DAT are over 10 μM. Thus, in general, their action on DAT could be negligible in clinics. The second reason is that these drugs are all currently used in clinics, mainly used for anti-depressant, and their safety and side effects have been well documented.

This result revealed that the rank order of potency for the three SERT inhibitors in attenuating abdominal stretching or yawning is citalopram=clomipramine>fluoxetine, and the relative ratio of EC_{50} for citalopram:clomipramine:fluoxetine is roughly 1:1:4 (5–10 mg/kg for citalopram, 5–10 mg/kg for clomipramine, 20–40 mg/kg for fluoxetine). Such rank order and relative ratio of inhibitory potency of these drugs are rather close to those measured by ligand binding analysis on SERT, in which the rank order of potency is citalopram ≅ clomipramine>fluoxetine, and the affinity ratio for citalopram:clomipramine:fluoxetine is roughly 1:0.7:2.8 (0.75 nM for citalopram, 0.5 nM for clomipramine, and 2 nM for fluoxetine) (Millan et al., 2001; Owens et al., 1997), and, are apparently unlike to that on NET since the rank order of potency of these drugs binding to NET is clomipramine>fluoxetine>citalopram, and the relative ratio of affinity for clomipramine:fluoxetine:citalopram is roughly 1:5:30 (100–200 nM for clomipramine, 500 nM for fluoxetine, and 3000 nM for citalopram). This comparison favors that the inhibitory effect of these three drugs in naloxone-precipitated withdrawal syndrome is through their inhibition on SERT but not on NET.

Previous reports had proved that serotonin system is one of the earliest neurotransmission systems 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, such as clomipramine, did alter the function of the serotonin-mediated neurotransmission (Hansen and Mikkelsen, 1998; Foguet et al., 1993). These reports further support the notion that these SERT inhibitors could act at SERT in neonatal rat brain.

It appears that the potency of the three examined SERT inhibitors in attenuating naloxone-precipitated yawning behavior is significantly higher than that in attenuating abdominal stretching behavior since 20 mg/kg of fluoxetine could have apparent effect in suppressing yawning, but only have mild effect on abdominal stretching, and, 2 mg/kg of clomipramine or citalopram could completely abolish the yawning behaviors, but 10 mg/kg of these two drugs is required to abolish abdominal stretching. The mechanism responsible for the higher sensitivity of these three drugs in abolishing yawing behavior is not clear at present. But, it is likely that such effectiveness of these three drugs in yawning behavior is still dependent on their blocking effect on the SERT rather than on the NET or DRT since the rank order of potency of these three drugs in abolishing yawning is similar to that in abdominal stretching, and, to block NET or DAT requires much higher concentration of these drugs than to block SERT. In addition, previous report had found that activation of serotonin receptor subtype, 5-HT_{1A} receptor or 5-HT_2 receptor, serves as an inhibitory mechanism for yawning response (Argiolas and Melis, 1998). However, the role of dopamine system or norepinephrine system is not identified yet.

The result of this study is consistent with the study of SERT inhibitor on morphine withdrawal syndrome in adult rats (El-Kadi and Sharif, 1995; Lu et al., 2001; Rafieian-Kopaei et al., 1995), indicating that serotonin-mediated transmission plays a significant role in the expression of acute morphine withdrawal syndrome in both adult and neonatal rats. Thus, either a deficiency in the serotonin-mediated neurotransmission, which contributes to the expression of withdrawal syndrome, or an increase in serotonin function, which counteracts the mechanisms responsible for the expression of morphine withdrawal

syndrome, could explain the therapeutic effect of the SERT inhibitors. 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 that the neural pathway responsible for withdrawal syndrome is far more complicated. Both glutamate and serotonin neurotransmitter systems might functionally converge in the neural network in generation of the withdrawal syndrome. It might be that the functions of these two systems are altered in an 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 not be changed at all in the 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.

In summary, the present study supports that SERT inhibitors are of potential in treating the acute morphine withdrawal syndrome in newborn baby. However, any therapeutics use of SERT inhibitors in newborn stage still requires more accurate evaluation of all possible adverse effect and justification of the risk-benefit ratio.

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