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The involvement of endogenous opioid mechanisms in the antinociceptive effects induced by antidepressant drugs, desipramine and trimipramine

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Abstract

The present study was designed to investigate the involvement of endogenous opioid systems in the antinociception induced by the antidepressant drugs, desipramine and trimipramine. For this purpose, the antinociceptive effects of desipramine (7.5 and 15.0 mg/kg i.p.) and trimipramine (5.0 and 10.0 mg/kg i.p.) were compared to that induced by morphine (0.2 and 2.0 mg/kg i.p.) in the tail-clip model in mice. Naloxone (0.3 and 3.0 mg/kg i.p.), a non-specific opioid receptor antagonist, inhibited morphine-induced antinociception in mice, whereas the antinociceptive effects of antidepressant drugs were found to be resistant to naloxone blockade to some extent, since only the higher concentration of naloxone (3.0 mg/kg i.p.) caused significant inhibition of the effects of antidepressant drugs. In contrast, naltrindole (1.0 mg/kg i.p.), a specific δ-receptor antagonist, inhibited antinociception induced by desipramine and trimipramine in this test, while it inhibited the antinociceptive effect of morphine only partly. None of the opioid antagonists produced a significant effect in the tail-clip experiment when they were injected alone. Based on these findings, we concluded that endogenous opioids are involved in the antinociceptive effects of the antidepressant drugs using different mechanisms.

Keywords: Desipramine; Trimipramine; Morphine; Opioid receptors; Antinociception

1. Introduction

Although the main clinical indication of tricyclic drugs is the treatment of depression and related disorders, administration of antidepressant drugs has been shown to affect the pain perception in human beings (McQuay et al., 1997; Chen et al., 2004; Fine et al., 2004) and in experimental animals (Rigal et al., 1983; Schreiber et al., 1998, 2000, 2002a,b). It has been shown that the acute administration of antidepressant drugs to rodents induces antinociception (Eschalier et al., 1981; Rigal et al., 1983; Schreiber et al., 1998; Nayebi et al., 2001) and potentiates antinociceptive activity of opioids (Lee and Spencer, 1980; Nayebi et al., 2001). Similar antinociceptive activities and potentiation of opioid antinociception have also been demonstrated in human (McQuay et al., 1997; Carter and Sullivan, 2002; Chen et al., 2004).

In spite of the fact that various antidepressants have been extensively used as an alternative of narcotic analgesics to treat chronic pain in man, responsible mechanisms for their antinociceptive effects upon acute administration have not been fully understood. The interferences of tricyclic antidepressant drugs with monoamine (norepinephrine, 5-HT, etc.) turnover in the central nervous system have been widely accepted as essential responsible mechanisms for their antidepressant actions (Bonhomme and Esposito, 1998; Pacher and Kecskemeti, 2004). These mechanisms also seem to be involved in their antinociceptive actions (Carter and Sullivan, 2002). However, there may be some additional endogenous mechanisms contributing antinociceptive actions of the antidepressant drugs, such as the inhibition of ion channels, inhibition of neuronal adenosine uptake, binding to NMDA receptor complex, inhibition of α-adrenergic, muscarinic, nicotinic and histaminic receptors, activation of α_2-adrenergic receptors and

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opioid system (Antkiewicz-Michaluk et al., 1991; Gray et al., 1999; Ghelardini et al., 2000; Sudoh et al., 2003). Although antinociception induced by tricyclic antidepressant drugs have been reported to possess peripheral, spinal and central nerve components (Carter and Sullivan, 2002; Sudoh et al., 2003), it remains unclear, which of these known mechanisms produce specific antinociceptive effects, or to what extent a particular mechanism causes antinociception.

Endogenous opioid system has a particular importance for the antinociceptive actions of tricyclic antidepressant drugs, since this system is the most effective mechanism in the modulation of pain. It has been reported that the potentiation of the antinociceptive effect of morphine by tricyclic antidepressant drugs is not due to a pharmacokinetic interaction (Bianchi et al., 1988). Tricyclic antidepressant drugs have been reported to enhance morphine tolerance (Lee and Spencer, 1980). Although a number of animal studies have reported the inhibition of antinociceptive effects of tricyclic antidepressant drugs with naloxone pretreatment (Eschalier et al., 1981; Isenberg and Cicero, 1984; Sacerdote et al., 1987; Ardid and Guilbaud, 1992; Gray et al., 1998; Marchand et al., 2003), only a few studies have indicated naltrindole-induced inhibition of antinociceptive effects of antidepressant drugs (Gray et al., 1998; Marchand et al., 2003). Furthermore, acetorphan, an enkephalinase inhibitor, has been reported to potentiate antinociceptive effects of antidepressant drugs (Gray et al., 1998). Other studies have shown that chronic administration of antidepressant drugs may decrease the number of cerebrocortical opioid receptors (Reisine and Soubrie, 1982) and increase enkephalin levels in nucleus accumbens and striatum in rats (De Felipe et al., 1985). Increases in the rat hypothalamic β-endorphin concentrations have been reported after the acute and chronic administration of tricyclic antidepressant drugs (Sacerdote et al., 1987). It has also been reported that tricyclic antidepressants may induce lipid modification and opioid binding in the membrane of glioma C6 cells (Albouz et al., 1982) and brain homogenates of rats (Isenberg and Cicero, 1984). From these findings, endogenous opioid mechanisms seem to be involved in the antinociceptive activity of antidepressant drugs. The primary aim of the present study was to investigate the involvement of endogenous opioid mechanisms in the antinociceptive activity of antidepressant drugs by using opioid antagonists, naloxone and naltrindole.

2. Materials and methods

Inbred Male Swiss Albino mice of local strain, weighing 30 to 45 g, were used. Starting at least 1 week prior to the beginning of the experimental period, they were housed 10 per cage, given food and tap water ad libitum and kept in a well-ventilated room at a temperature of 20±3 °C. All mice were fed with a standard diet. Antinociception in mice was measured by the tail-clip method as described earlier (D'Amour and Smith, 1941; Aydın et al., 1998). Briefly, a commercial arterial clamp was clipped to the tail. The time that elapsed until the animal turned and tried to bite the clamp was taken as the antinociceptive latency. Before administration of drugs, the clamp test was repeated two to three times with resting periods between tests to establish the baseline for the antinociceptive response. At the final trial, animals that showed latencies of more than 4 s were discarded. The maximal cut off time was 20 s. Animals with latency longer than 5 s after treatment with test compound were regarded as showing antinociception. All the drugs, administered intraperitoneally 30 min before the tail-clip procedure, were dissolved in 0.9% physiological saline solution. Controls received only saline solution. Morphine sulfate (Sigma, St. Louis, USA) at doses of 0.2 and 2.0 mg/kg, desipramine hydrochloride (Sigma, St. Louis, USA) at 7.5 and 15.0 mg/kg, trimipramine maleate (Servier, Paris, France) at 5.0 and 10.0 mg/kg, naloxone hydrochloride (Sigma, St. Louis, USA) at 0.3 and 3 mg/kg and naltrindole hydrochloride (Sigma, St. Louis, USA) at a dose of 1.0 mg/kg were administered by intraperitoneal injections. In each case, injection volume did not exceed 0.2 ml. Opioid antagonists (naloxone and naltrindole) were injected 15 min prior to the administration of morphine or antidepressant drugs, desipramine and trimipramine. The dosages for antinociceptive drugs (morphine, desipramine and trimipramine) and opioid antagonists (naloxone and naltrindole) were chosen according to the literature data. Tail-clip latencies expressed in seconds were reported as the mean of at least five measurements in each experimental group with ±standard error (S.E). The statistical differences between latencies measured experimentally were evaluated by one-way ANOVA (analysis of variance) (Finney, 1978).

3. Results

3.1. Effects of morphine

Mice injected with morphine (0.2 and 2.0 mg/kg i.p.) exhibited statistically significant prolongation of tail-clip latencies indicating an obvious antinociceptive effect (Fig. 1). Morphine-induced antinociception was almost completely abolished in mice pretreated with naloxone (Fig. 2), although naltrindole pretreatment caused only a moderate and statistically significant inhibition in the morphine antinociception at 2.0 mg/kg (Fig. 3).

3.2. Effects of antidepressant drugs

Antidepressant drugs, desipramine and trimipramine, caused statistically significant prolongation in the tail-clip latency of mice suggesting antinociception. There were no indications of sedation in animal groups injected with desipramine and trimipramine. Antinociceptive effects induced by antidepressant drugs were comparable to morphine effects in magnitude (Fig. 1). Naloxone was found to be ineffective on the antinociception induced by desipramine (Fig. 4). Naloxone at low dose (0.3 mg/kg) caused an increase in the antinociceptive activity of trimipramine, while its high dose (3.0 mg/kg) completely inhibited trimipramine-induced antinociception (Fig. 5). However, pretreatment of mice with naltrindole resulted in inhibition of desipramine-induced antinociception (Fig. 6). Naltrindole inhibited only the antinociception induced by 10 mg/kg

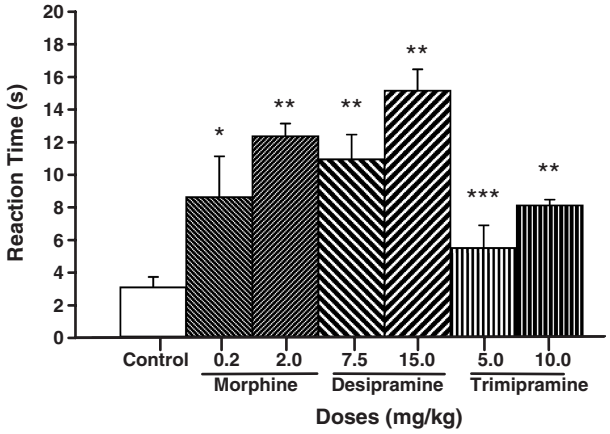

Fig. 1. Effects of morphine, desipramine and trimipramine on the tail-clip latency of mice. *$p<0.05$, **$p<0.005$ and ***$p<0.10$ statistical significances relative to control. Vertical bars indicate ± S.E. ($n=5$ in each group).

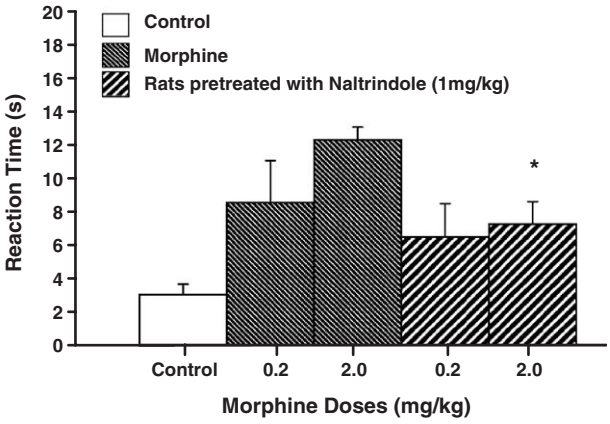

Fig. 3. Effect of naltrindole pretreatment on the antinociception induced by morphine in mice as measured by the tail-clip experiments. *$p<0.05$ statistical significance relative to treatment with 2.0 mg/kg morphine alone. Vertical bars indicate ±S.E. ($n=5$ in each group).

trimipramine, while it was ineffective against the antinociceptive effect of 5 mg/kg trimipramine (Fig. 7).

3.3. Effects of opioid antagonists

In the present study, we employed two different doses of naloxone, since it is a non-specific opioid receptor antagonist and it is able to block different opioid receptor subtypes at different doses. When the opioid antagonists, naloxone (0.3 and 3 mg/kg) and naltrindole (1.0 mg/kg) were administered alone, no change was observed in the tail-clip test on mice (Fig. 8).

4. Discussion

Tricyclic antidepressant drugs have been reported to exhibit antinociceptive properties in neuropathic, nociceptive and inflammatory models of pain (Carter and Sullivan, 2002). Among the large number of animal models of acute and chronic pain (Le Bars et al., 2001; Martin and Eisenach, 2001), there are certain tests as experimental models of pain, in which tricyclic antidepressants have been extensively studied: tail flick, hot-plate and formalin tests, all of which possess behavioral components in response to nociception. Tail-clip is a variant of tail-flick test, which comprises mechanical stimuli instead of thermal ones. Both tail flick and hot plate tests comprise phasic pain due to short duration of (acute) noxious stimuli, while formalin test measure tonic pain due to long duration of (persistent) noxious stimuli (Le Bars et al., 2001). Tricyclic antidepressant drugs, nortryptiline, desipramine and imipramine, have been found to be effective on the pain in rat formalin test (Sawynok and Reid, 2001). Using hot plate tests in mice, Schreiber et al. (1996, 1998, 2000, 2002a,b) have reported antinociceptive effects of a series of antidepressant drugs. There are also a number of reports indicating the antinociceptive properties of tricyclic antidepressants in tail flick test (Uzbay et al., 1999; Rojas-Corrales et al., 2003; Özdogan et al., 2004). In agreement with the previous reports, findings obtained in the present study indicated that desipramine and trimipramine at applied doses possess antinociceptive effects without sedation in mice. Sedative actions of these two drugs have been noticed in previous studies from our laboratory reporting decreases in

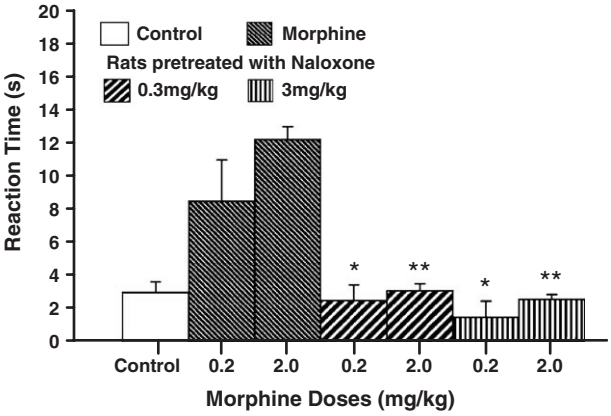

Fig. 2. Effect of naloxone pretreatment on the antinociception induced by morphine in mice as measured by the tail-clip experiments. *$p<0.05$ and **$p<0.005$ statistical significances relative to treatments with 0.2 and 2.0 mg/kg morphine alone, respectively. Vertical bars indicate ±S.E. ($n=5$ in each group).

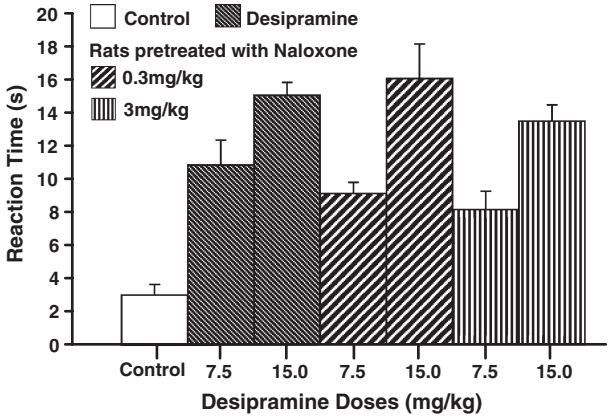

Fig. 4. Effect of naloxone pretreatment on the antinociception induced by desipramine in mice as measured by the tail-clip experiments. Vertical bars indicate ±S.E. ($n=5$ in each group).

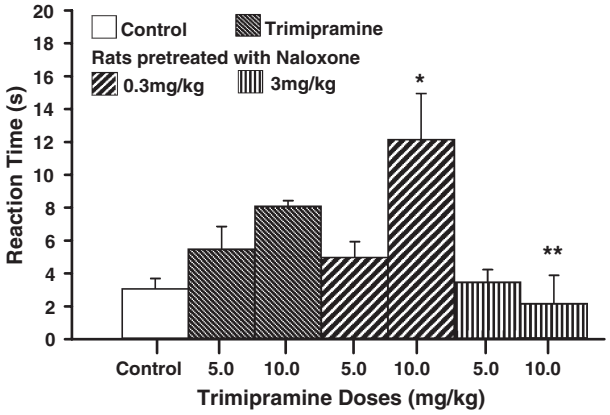

Fig. 5. Effect of naloxone pretreatment on the antinociception induced by trimipramine in mice as measured by the tail-clip experiments. *$p<0.05$ and **$p<0.005$ statistical significances relative to treatment with 10.0 mg/kg trimipramine alone. Vertical bars indicate ±S.E. ($n=5$ in each group).

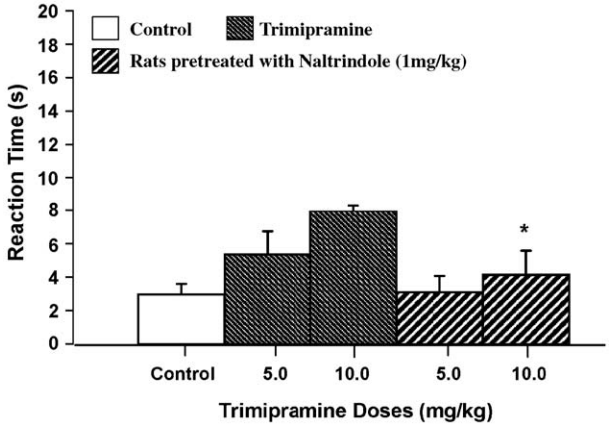

Fig. 7. Effect of naltrindole pretreatment on the antinociception induced by trimipramine in mice as measured by the tail-clip experiments. *$p<0.05$ statistical significance relative to treatment with 10.0 mg/kg trimipramine alone. Vertical bars indicate ±S.E. ($n=5$ in each group).

locomotor activity of mice and immobility time of swimming test at a dose level higher than 30 and 20 mg/kg for desipramine and trimipramine, respectively (Öztürk et al., 1996a,b,c). Therefore, the prolonged reaction time following desipramine or trimipramine-treatment seems to be due to their antinociceptive actions rather than a sedative effect. Our results showed that the antinociception produced by desipramine was not inhibited by naloxone at the dose that inhibited completely the antinociceptive effect of morphine (Fig. 4). The antinociception induced by trimipramine was also found to be resistant to the low dose of naloxone. In fact, 0.3 mg/kg of naloxone did not inhibit the effect of trimipramine on tail-clip response of mice (Fig. 5), whereas the same dose of naloxone almost completely abolished the effect of morphine (Fig. 2).

The present study also revealed that the antinociceptive effects of desipramine and trimipramine have differences in terms of the involvement of opioid mechanisms. These differences may also be related to the differences in the antidepressant actions of desipramine and trimipramine as reported in previous studies. Desipramine mainly affects norepinephrine uptake (Rojas-Corrales et al., 2003), whereas trimipramine does not block the reuptake of noradrenaline or that of 5-HT, does not increase the evoked release of [^{3}H] noradrenaline and does not desensitize the 5-HT$_3$ receptors (Mongeau et al., 1994). However, most probably related to its antidepressant action, trimipramine has been reported to have a weak effect on the central noradrenergic system, activate locus coeruleus neurons and produce a reduction in the depressant action of noradrenaline administered iontophoretically to neurons in the cingulate cortex (Hauser et al., 1985). Previous studies have also indicated similar differences in the involvement of opioid mechanisms in the antinociceptive responses to various antidepressant drugs. For instance, it has been reported that κ- and μ-opioid receptors are involved in mianserin-induced antinociception (Schreiber et al., 1998), while only μ-receptors play a role in the antinociceptive responses to trazodone (Schreiber et al., 2000). Similar to mianserin, mirtazapine-induced antinociception seems to be mediated both by κ- and μ-opioid receptors (Schreiber et al., 2002a,b),

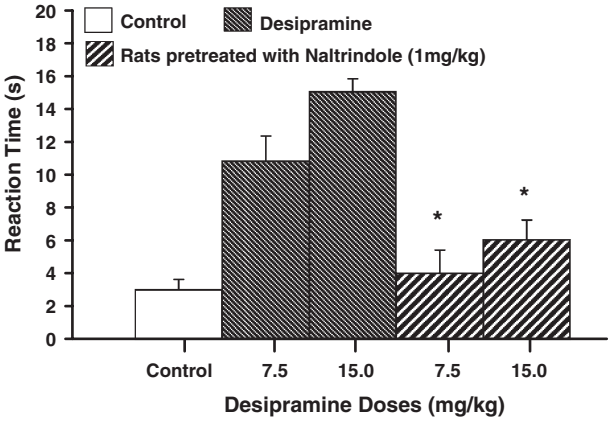

Fig. 6. Effect of naltrindole pretreatment on the antinociception induced by desipramine in mice as measured by the tail-clip experiments. *$p<0.005$ significances relative to treatments with 7.5 and 15.0 mg/kg desipramine alone. Vertical bars indicate ±S.E. ($n=5$ in each group).

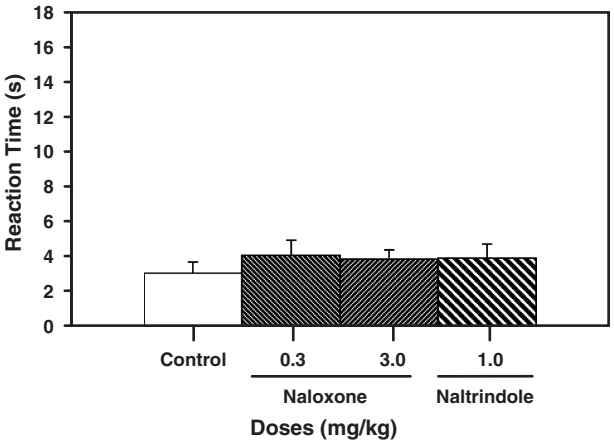

Fig. 8. Effects of naloxone and naltrindole on the tail-clip latency of mice. Vertical bars indicate ±S.E. ($n=5$ in each group).

whereas all three opioid receptor subtypes seem to play a role in antinociceptive responses of mice to fluvoxamine and venlafaxine (Schreiber et al., 1996, 2002a). The magnitude of antinociceptive activity of desipramine seems to be higher than that of trimipramine (Fig. 1). Naloxone did not cause a statistically significant change in the antinociceptive activity of desipramine (Fig. 4), while the antinociception induced by 10 mg/kg trimipramine was increased by the low dose of naloxone and decreased by high dose of this opioid antagonist (Fig. 5). From these findings, it may be speculated that μ-opioid receptors play a role the antinociceptive response of mice to trimipramine, but not to desipramine.

Although μ-, δ- and κ-subtypes of opioid receptors are involved in the morphine-induced antinociception (Przewlocki et al., 1983; Ward and Takemori, 1983; Schmauss and Yaksh, 1984), morphine has been reported to have an approximately 50-fold higher affinity for μ- than for δ-receptors (Emmerson et al., 1994). On the other hand, low doses of naloxone have been reported to block μ-subtype of opioid receptors, while its higher doses may block other opioid receptor subtypes (Dhawan et al., 1996). Therefore, it is not surprising that naloxone caused a strong inhibition in the antinociceptive effect of morphine on mice (Fig. 2), whereas naltrindole, specific δ-receptor antagonist, caused only a moderate inhibition (Fig. 3). Naltrindole caused only a moderate inhibitory effect in the trimipramine-induced antinociception, while it caused strong inhibitions in the antinociception induced by desipramine suggesting that δ-opioid receptor activation may also be involved in the antinociceptive effects of desipramine. As an evidence supporting this suggestion, δ-receptor activation has been reported to increase locomotor activity and induce antidepressant-like effects (Baamonde et al., 1992; Broom et al., 2002) and mice lacking the δ-receptor has been shown to display behavior consistent with a depressive profile (Filliol et al., 2000). However, further studies may be required for understanding the exact role of opioid receptors in the antinociception induced by antidepressant drugs whose mechanisms of action include different physiological mechanisms such as serotonergic, noradrenergic systems, etc.

It is also interesting that the antinociceptive effect at high doses of trimipramine was potentiated significantly by the pretreatment with 0.3 mg/kg naloxone (Fig. 5). This potentiation may be due to the intrinsic antinociceptive activity of naloxone, which has been reported previously in various studies (Levine et al., 1979; Ueda et al., 1986). A similar phenomenon has been reported with naloxone and naltrexone, non-specific opioid antagonists, upon their administrations at ultra-low doses (10 ng/kg i.p.) to mice and rats, respectively (Powell et al., 2002). The augmentation of trimipramine antinociception by low doses of naloxone may be due to block of opioid-induced hyperalgesia. Most probably, this may result from excitatory effects of opioids at very low doses.

In conclusion, the present study demonstrated that the antidepressant drugs desipramine and trimipramine exhibit antinociceptive actions in mice through a mechanism related to endogenous opioids. In addition, δ-opioid receptors seem to be involved in this mechanism for both desipramine and trimipramine, while μ-opioid receptors exhibit complex effects of trimipramine.

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