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Fluoxetine attenuates thermal hyperalgesia through 5-$HT_{1/2}$ receptors in streptozotocin-induced diabetic mice

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Abstract

Diabetic neuropathic pain, an important microvascular complication in diabetes mellitus, is recognised as one of the most difficult types of pain to treat. A lack of understanding of its aetiology, inadequate relief, development of tolerance and potential toxicity of classical antinociceptives warrant the investigation of newer agents to relieve this pain. The aim of the present study was to explore the antinociceptive effect and possible mechanism of action of a serotonin reuptake inhibitor, fluoxetine, in streptozotocin-induced diabetic mice. Four weeks after a single intraperitoneal injection of streptozotocin (200 mg/kg), mice were tested in the tail-immersion and hot-plate assays. Diabetic mice exhibited significant hyperalgesia compared with control mice. Fluoxetine (10 and 20, but not 5 mg/kg, i.p.) injected into diabetic mice produced an antinociceptive effect in both the tail-immersion and hot-plate assays. The percentage maximum possible effect (% MPE) produced by fluoxetine (20 mg/kg, i.p.) was significantly lower in diabetic mice than in control mice. The antinociceptive effect of fluoxetine (20 mg/kg) in diabetic mice was dose-dependently potentiated by pindolol (5 and 10 mg/kg, i.p., a selective 5-$HT_{1A/1B}$ receptor antagonist), attenuated by ritanserin (1 and 2 mg/kg, i.p., a selective 5-$HT_{2A/2C}$ receptor antagonist) and remained unaffected by ondansetron (1 and 2 mg/kg, i.p., a selective 5-HT_3 receptor antagonist) in both test systems. These results suggest that fluoxetine-induced antinociception primarily involves serotonin pathway modulation through 5-HT_1 and 5-HT_2 receptors, but not through 5-HT_3 receptors, in the chronic pain associated with streptozotocin-induced diabetic neuropathy. Further, the potentiation of the antinociceptive effect of fluoxetine by pindolol indicates the usefulness of a combination of an antidepressant and a 5-$HT_{1A/1B}$ receptor antagonist in the treatment of diabetic neuropathic pain in humans.

Keywords: Antidepressant; Hot-plate; Fluoxetine; Neuropathic pain; Streptozotocin; Tail-immersion

1. Introduction

Neuropathic pain is generally considered to be one of the most common complications of diabetes, affecting both types of diabetes equally (Clark and Lee, 1995; Vinik et al., 1992; Watkins, 1990). It is mostly characterized by pain which can occur spontaneously as a result of exposure to normally mildly painful stimuli, i.e. hyperalgesia (Brown and Asbury, 1984). Although hyperglycaemia (Greene et al., 1987), neuronal loss (Dyck et al., 1985; Said et al., 1992) or neurotransmitter changes (Bellush and Reid, 1991; Bitar et al., 1985; Chu et al., 1986) have been reported to be responsible for the change in pain perception, the exact aetiological factors involved are still under investigation.

The behavioural reaction to hyperalgesia has been described in animal models of diabetes (Anjaneyulu and Chopra, 2003; Courteix et al., 1993; Forman et al., 1986; Kamei et al., 1991; Lee and McCarty, 1990). Streptozotocin-induced diabetic mice have been widely used as a model of diabetes mellitus, and a number of anomalies in pain perception have been demonstrated in this model (Kamei et al., 2000). Chemical-induced flinching, thermal hyperalgesia and allodynia have been observed in streptozotocin-treated mice (Kamei et al., 2001; Ohsawa and Kamei, 1999).

5-Hydroxytryptamine (5-HT) is widely accepted as an important neurotransmitter participating in the central and

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spinal inhibition of nociceptive transmission (Bardin et al., 2000; Zhang and Wu, 2000). Behavioural studies have demonstrated that 5-HT is implicated in the control exerted by the brain on nociception either by afferent fibre hyperpolarization or through a presynaptic action. Serotonergic deficiency is a common factor in both mental depression and chronic pain (Vogel et al., 2003; Sounvoravong et al., 2004). It has been reported that destruction of serotonergic projections greatly affects nociception. In contrast, increasing the availability of 5-HT at the synapse is reported to inhibit nociception by acting at spinal cord, brainstem or thalamic levels.

Several 5-HT receptor subtypes mediate antinociception (Hoyer et al., 1994; Obata et al., 2001). Although controversy exists, 5-$HT_{1A/1B}$, 5-HT_2 and 5-HT_3 receptors have been reported to be involved in the spinal antinociceptive effect of 5-HT (Eide and Hole, 1993). Previous studies, however, investigated the spinal antinociceptive effect of 5-HT receptor subtypes in acute pain models, but much less is known about which 5-HT receptor subtypes are involved in chronic pain, such as neuropathic pain associated with diabetes. It has also been found that 5-HT receptor antagonists inhibit the antinociceptive effect of some antidepressants, such as clomipramine (Eschalier et al., 1981), amitriptyline or imipramine (De Felipe et al., 1986).

Against this background, the aim of the present study was to investigate the antinociceptive action of a selective serotonin reuptake inhibitor, fluoxetine, and to explore the involvement of 5-HT receptor subtypes in diabetic neuropathic pain.

2. Material and methods

2.1. Animals

Male albino mice of the Laka strain (20–30 g) bred in the Central Animal House facility of Panjab University were used in the present study. The animals were housed under optimal laboratory conditions, maintained on a natural light and dark cycle, and had free access to food and water ad libitum. Animals were acclimatized to laboratory conditions before the test. All experiments were carried out blindly between 09:00 and 17:00 h. The experimental protocols were approved by the Institutional Animal Ethics Committee and conducted according to the Indian National Science Academy Guidelines for the use and care of animals (licence number: 388/Ethic/2002).

2.2. Drugs and reagents

Streptozotocin and pindolol were purchased from Sigma (St. Louis, MO, USA). Fluoxetine (gift sample from Divis Pharma, India), ondansetron (gift sample from Cipla, India) and pindolol were dissolved in distilled water. Ritanserin (gift sample from Janssen Research Foundation, Belgium) was dissolved in one drop of concentrated hydrochloric acid, the pH was adjusted to neutral and the volume was made up with distilled water. The glucose oxidase peroxidase enzyme kit was purchased from Span Diagnostics, India.

2.3. Induction and assessment of diabetes

Streptozotocin was prepared in citrate buffer (pH 4.4, 0.1 M) (Banisinath et al., 1988) and injected intraperitoneally in a single dose of 200 mg/kg (Ramabadran et al., 1989). The age-matched control mice received an equivalent volume of citrate buffer. Plasma glucose levels were estimated at 2 days and 4 weeks after streptozotocin injection with the glucose oxidase peroxidase diagnostic kit method (Schmidt, 1971). About 90% of streptozotocin-injected mice had plasma glucose levels of more than 250 mg/dl (Anjaneyulu and Ramarao, 2002) and these mice were used for the present study after 4 weeks.

2.4. Treatment schedule

At the end of 4 weeks, control and diabetic mice were randomly divided into different groups consisting of six to seven animals. Preliminary thresholds for the tail-immersion and hot-plate response (the mean of two consecutive stable values which do not differ more than 10%) were determined before drug administration. Fluoxetine (5, 10 and 20 mg/kg) was administered intraperitoneally in three groups of diabetic mice after measurement of baseline responses. One control group was also treated with a higher dose of fluoxetine (20 mg/kg) in order to compare the potency between control and diabetic mice. In other groups of diabetic mice, the 5-HT receptor antagonists, pindolol (5 and 10 mg/kg), ritanserin (1 and 2 mg/kg) and ondansetron (1 and 2 mg/kg), were injected intraperitoneally 5 min before the fluoxetine (20 mg/kg) injection. In diabetic mice, serotonin receptor antagonists were also injected. In both tail-immersion and hot-plate assays, nociceptive latency was measured at 15, 30, 60 and 180 min after fluoxetine injection and expressed as the percentage of the maximum possible effect (% MPE), where the % MPE=(post-drug threshold-pre drug threshold)×100/(cut-off time-pre drug threshold). All drug solutions were freshly prepared and injected intraperitoneally in a constant volume of 1 ml/100 g of body weight.

2.5. Assessment of thermal hyperalgesia

2.5.1. Tail-immersion (warm water) test

The tail was immersed in a warm water bath (52.5±0.5 °C) until tail withdrawal (flicking response) or signs of struggle were observed (cut-off 12 s). The hyperalgesic response in the tail-withdrawal test is generally attributed to central mechanisms (Kannan et al., 1996; Ramabadran et al., 1989).

Table 1
General parameters in streptozotocin-induced diabetic mice

	Basal	1 week	2 weeks	3 weeks	4 weeks
Body weight (g)	26±1.56	22.6±1.39[a]	20±1.73[a]	17.6±1.25[a]	15.4±1.46[a]
Tail-flick (s)	4.27±0.34	2.68±0.7[a]	1.84±0.25[a]	1.4±0.41[a]	1.35±0.32[a]
Hot-plate (s)	4.35± 0.52	3.56±0.22	2.56±0.25[a]	1.54±0.4[a]	1.36±0.21[a]

Data are the means±S.E.M.
[a] $P<0.001$ as compared with its basal values.

2.5.2. Hot-plate test

The hyperalgesic response on the hot-plate is considered to result from a combination of central and peripheral mechanisms (Kannan et al., 1996). In this test, animals were individually placed on a hot-plate (Eddy's Hot-Plate) with the temperature adjusted to 55±1 °C. The latency to the first sign of paw licking or jump response to avoid the heat was taken as an index of the pain threshold; the cut-off time was 10 s in order to avoid damage to the paw.

2.6. Statistical analysis

The nociceptive threshold, i.e. the latency (in seconds) to thermal noxious stimulus, was measured and the % MPE was calculated. The data are expressed as means±S.E.M. The hyperalgesic response was analysed by analysis of variance followed by Tukey's *t*-test. Student's unpaired *t*-test was used to compare the values from two groups. $P<0.05$ was considered as significant.

3. Results

3.1. Effect of streptozotocin-injection on blood glucose and body weight

Four weeks after streptozotocin injection, the diabetic mice had significantly higher blood glucose levels (465.26±22.46 mg/dl) than the control mice (112.42±14.72 mg/dl; $P<0.001$). There was a marked decrease in the body weight of streptozotocin-injected mice

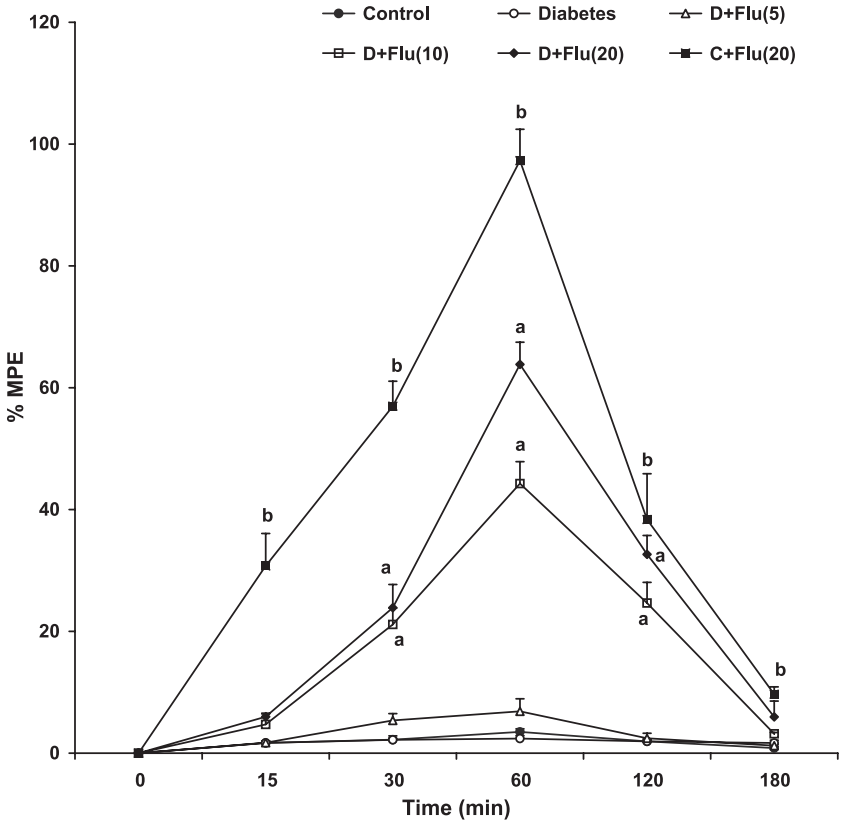

Fig. 1. Effect of fluoxetine on tail-immersion nociceptive threshold in control and streptozotocin-induced diabetic mice. FLU(5): fluoxetine (5 mg/kg); FLU(10): fluoxetine (10 mg/kg); FLU(20): fluoxetine (20 mg/kg). Data are the means±S.E.M ($n=7$ in each group). [a]$P<0.001$ as compared with diabetic mice at the respective times; [b]$P<0.001$ as compared with control mice at the respective times.

(17.4±1.35 g) as compared with control mice (28±3.46 g; $P<0.001$).

3.2. Effect of streptozotocin injection on nociceptive threshold

The nociceptive threshold was significantly lower in diabetic mice as compared with the basal value tested in both the tail-immersion and hot-plate assays. Hyperalgesia was evident in the tail-immersion and hot-plate tests after 1 and 2 weeks, respectively, and the maximum decrease in pain threshold was observed at 4 weeks after streptozotocin injection in mice (Table 1).

3.3. Effect of fluoxetine on nociceptive threshold in control and streptozotocin-induced diabetic mice

Systemic administration of fluoxetine (10 and 20 mg/kg, but not 5 mg/kg) produced a significant decrease in % MPE in both the tail-immersion (Fig. 1) and hot-plate (Fig. 2) assays in diabetic mice. The % MPE produced by fluoxetine (20 mg/kg) was significantly lower in diabetic mice than in the control mice. The maximum % MPE was observed at 60 min after administration of fluoxetine in diabetic mice.

3.4. Effect of 5-HT receptor antagonists on antinociceptive action of fluoxetine in streptozotocin-induced diabetic mice

Prior administration of pindolol (5 and 10 mg/kg) before fluoxetine (20 mg/kg) in diabetic mice resulted in a significant dose-dependent potentiation of the % MPE of fluoxetine in both the tail-immersion (Fig. 3) and hot-plate (Fig. 4) assays as compared to that of the control (untreated) diabetic mice. Pretreatment with ritanserin (1 and 2 mg/kg) resulted in a dose-dependent attenuation of the antinociceptive effect of fluoxetine in the both tail-immersion (Fig. 3) and the hot-plate (Fig. 4) systems. Ondansetron (1 and 2 mg/kg) did not affect the fluoxetine-induced % MPE in either the tail-immersion (Fig. 3) or the hot-plate (Fig. 4) assay. Pindolol (10 mg/kg) per se produced a slightly increased % MPE, but this effect was not significantly different from the control (untreated diabetic mice). Both ritanserin and ondansetron did not have an effect in these assay systems in diabetic mice.

4. Discussion

In the present study, mice injected with streptozotocin exhibited significantly increased plasma glucose levels, urine output and decrease in body weight as compared with

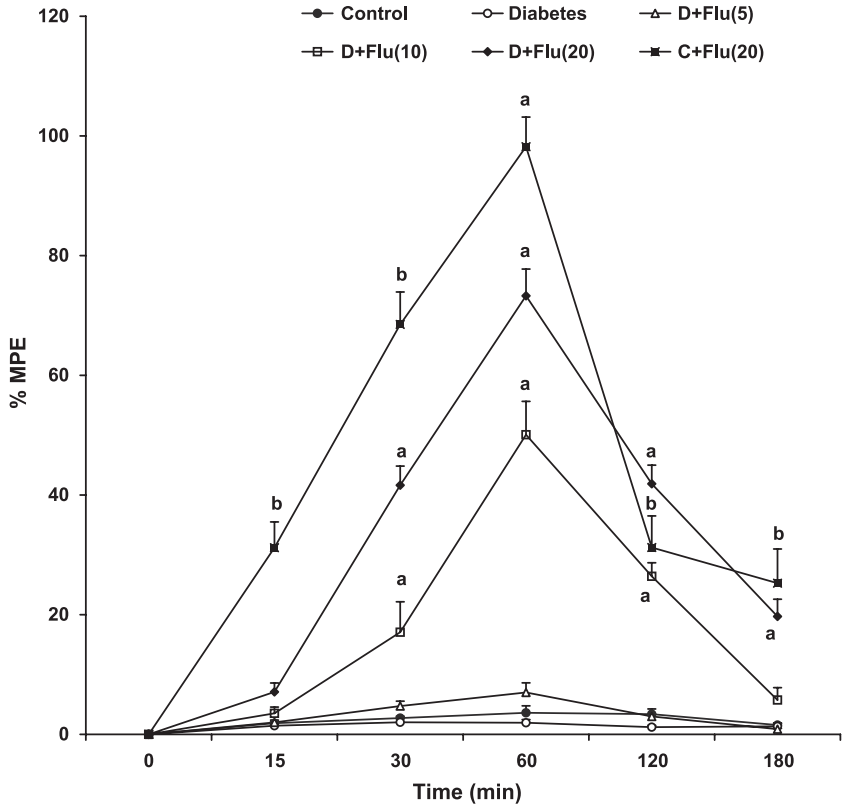

Fig. 2. Effect of fluoxetine on hot-plate nociceptive threshold in control and streptozotocin-induced diabetic mice. FLU(5): fluoxetine (5 mg/kg); FLU(10): fluoxetine (10 mg/kg); FLU(20): fluoxetine (20 mg/kg). Data are the means±S.E.M ($n=7$ in each group). [a]$P<0.001$ as compared with diabetic mice at the respective times; [b]$P<0.001$ as compared with control mice at the respective times.

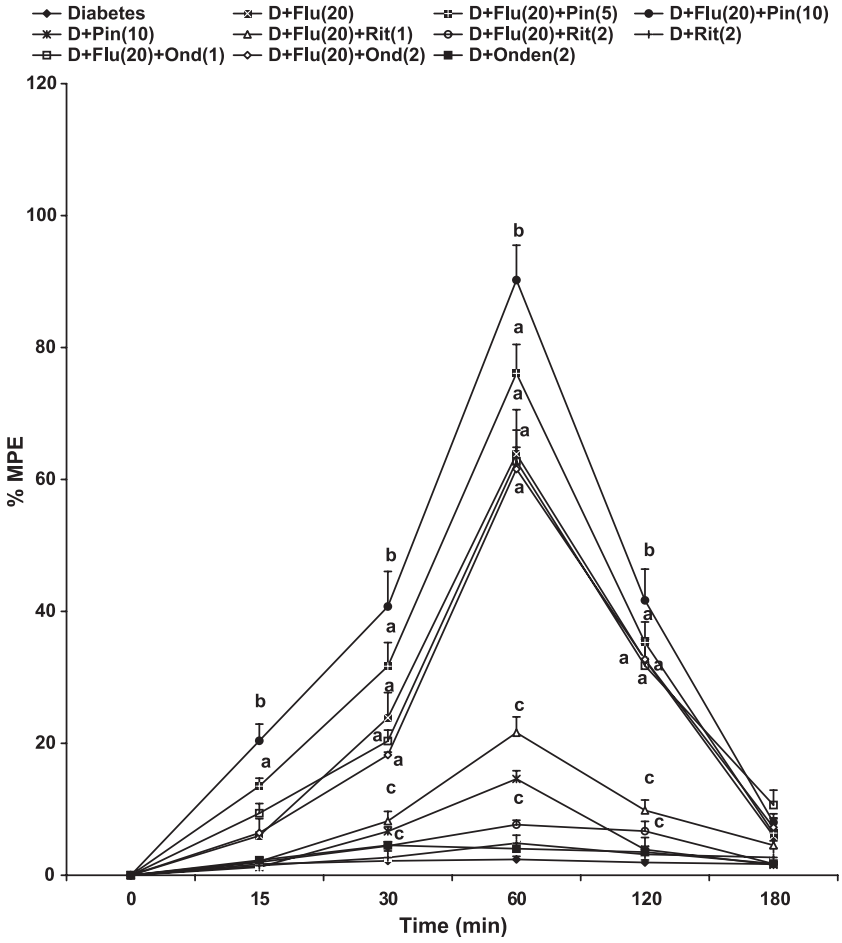

Fig. 3. Effect of fluoxetine and its combination with 5-HT receptor antagonists on tail-flick nociceptive threshold in streptozotocin-induced diabetic mice. FLU(10): fluoxetine (10 mg/kg); PIN(5): pindolol (5 mg/kg); PIN(10): pindolol (10 mg/kg); RIT(1): ritanserin (1 mg/kg); RIT(2): ritanserin (2 mg/kg); OND(1): ondansetron (1 mg/kg); OND(2): ondansetron (2 mg/kg). Data are the means±S.E.M (n=6 in each group). [a]P<0.001 as compared with diabetic mice. [b]P<0.001 as compared with diabetic, diabetic+fluoxetine (20) mice at the respective times. [c]P<0.001 as compared with diabetic+fluoxetine (20) mice at the respective times.

control mice. In diabetic mice, the tail-immersion latency was significantly shorter than that in non-diabetic mice, indicating that diabetic mice exhibit thermal hyperalgesia. This is in line with the observation of Ohsawa and Kamei (1999) that streptozotocin-induced diabetic mice exhibited thermal allodynia and hyperalgesia, tested by exposing the tail to noxious heating.

Streptozotocin-induced diabetic mice have been used as a model of chronic pain with signs of hyperalgesia and allodynia that may reflect symptoms observed in diabetic humans (Gul et al., 2000; Kamei et al., 2001). The altered pattern of nociception may not be due to the inherent neurotoxicity of streptozotocin (Calcutt and Chaplan, 1997), but instead the drug may induce a variety of pathophysiological symptoms that can lead to altered nociceptive responses tested in various animal models (Courteix et al., 1994; Hounsom and Tomlinson, 1997; Kamei et al., 2001).

In the present study, fluoxetine produced marked dose-dependent antinociception in control and streptozotocin-induced diabetic mice tested in the both tail-immersion and hot-plate assays. These results support earlier findings showing that systemic administration of fluoxetine produces antinociception in spinal nerve ligation, inflammation and other pain models (Filho and Takashi, 1999; Singh et al., 2001). The mechanisms of action of antidepressant-induced antinociception remain unclear; however, it is well known that the reuptake of monoamines is a major mechanism of their pharmacological action (Hyttel, 1994). The attenuation of diabetic hyperalgesia by fluoxetine in the tail-immersion and hot-plate systems indicates an important role of serotonergic modulation in the nociceptive response, because it is well documented that serotonergic antidepressants, such as fluoxetine, increase synaptic 5-HT levels.

The results of the present study also showed that fluoxetine was less potent in both the tail-immersion and hot-plate assays when it was administered alone in diabetic mice in comparison to its effect in control mice. Pretreatment with the putative 5-$HT_{1A/1B}$ receptor antagonist, pindolol significantly enhanced the fluoxetine-induced antinociception in both the tail-immersion and hot-plate assays in diabetic mice. This observation is in line with earlier reports showing that the antinociceptive action of an

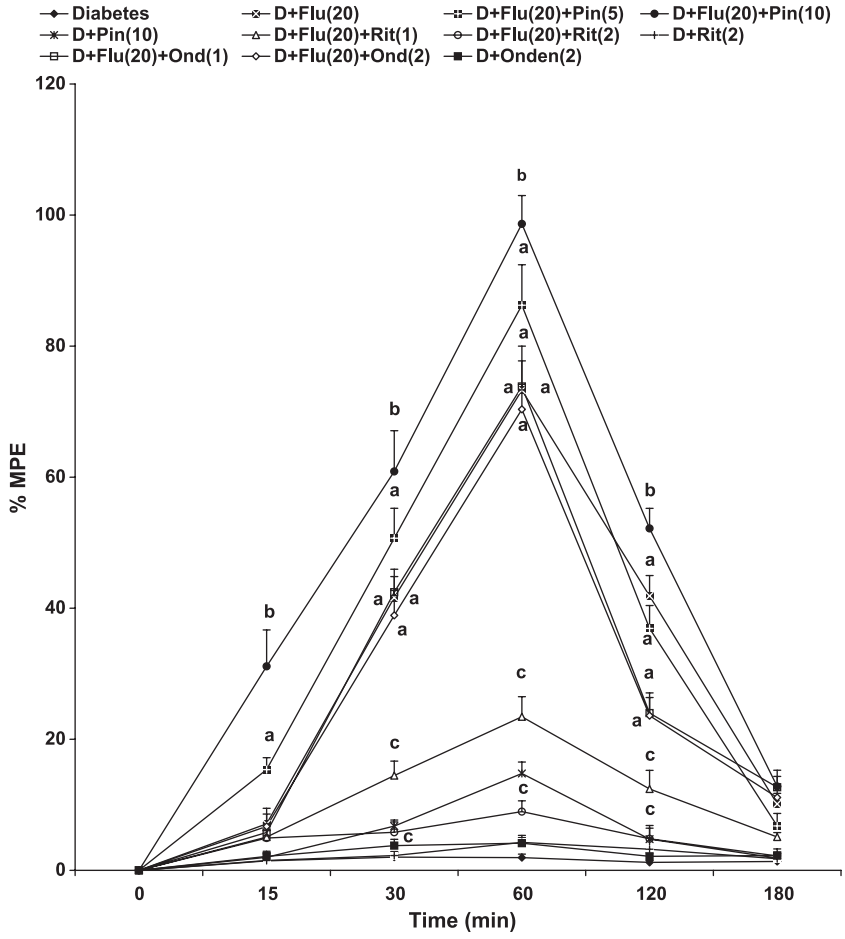

Fig. 4. Effect of fluoxetine and its combination with 5-HT receptor antagonists on hot-plate nociceptive threshold in streptozotocin-induced diabetic mice. FLU(10): fluoxetine (10 mg/kg); PIN(5): pindolol (5 mg/kg); PIN(10): pindolol (10 mg/kg); RIT(1): ritanserin (1 mg/kg); RIT(2): ritanserin (2 mg/kg); OND(1): ondansetron (1 mg/kg); OND(2): ondansetron (2 mg/kg). Data are the means±S.E.M (n=6 in each group). [a]P<0.001 as compared with control mice. [b]P<0.001 as compared with diabetic, diabetic+fluoxetine (20) mice at the respective times. [c]P<0.001 as compared with diabetic+fluoxetine (20) mice at the respective times.

antidepressant, clomipramine, was potentiated by the 5-HT_{1A} receptor antagonist in an animal model of neurogenic pain (Ardid et al., 2001). In our laboratory, pindolol has also been shown to increase the fluoxetine-induced antinociceptive effect in naïve animals in the acetic acid-induced writhing assay (Singh et al., 2001). Selective serotonin reuptake inhibitors when acutely administered show a delayed onset of action due to the indirect activation of autoreceptors following reuptake inhibition (Blier et al., 1990; Blier and De Montigny, 1994). In recent studies, pindolol has been found to accelerate or to enhance (Bjorvatin et al., 1998; Fornal et al., 1996) and attenuate (Rasmussen et al., 2004) the effect of selective serotonin reuptake inhibitors. Pindolol can also enhance 5-HT output even in the absence of selective serotonin reuptake inhibitors by directly acting at the level of the nerve terminal, and blockade of 5-$HT_{1A/1B}$ autoreceptors might account for the ability of pindolol to enhance 5-HT output (Fornal et al., 1999). This could be the reason for the slightly increased % MPE in diabetic mice after pindolol treatment alone. 5-HT_{1A} autoreceptors present at presynaptic sites are responsible for the inhibition of neuronal firing (Aghajanian, 1978) and thus axonal serotonin release (Adell and Artigas, 1991). Blockade of 5-HT_{1A} autoreceptors concomitant with administration of antidepressants induces a rapid rise in 5-HT in the terminal fields. Clinical studies performed in depressed patients have confirmed that co-administration of pindolol and antidepressants reduces the delay in action of thymolytic drugs and increases their efficacy (Perez et al., 1997; Tome et al., 1997).

In the present study, pretreatment with the selective 5-$HT_{2A/2C}$ receptor antagonist, ritanserin, but not with the 5-HT_3 receptor antagonist, ondansetron, dose-dependently attenuated the antinociceptive action of fluoxetine in diabetic mice in both the tail-immersion and hot-plate assays, indicating that 5-$HT_{2A/2C}$ but not 5-HT_3 receptors play an essential role in the attenuation of diabetic hyperalgesia by antidepressants. This is in support of an earlier study showing that meta-chlorophenylpiperazine, a 5-HT receptor agonist, inhibited formalin-induced nociceptive responses and chronic pain transmission in streptozotocin-induced diabetic and non-insulin dependent genetically

diabetic (db/db) mice through 5-HT_1 and 5-HT_2, but not 5-HT_3 receptors (Takeshita and Yamaguchi, 1995). Another study reports that intrathecal administration of a 5-HT_2, but not a 5-HT_3, receptor agonist produced an anti-allodynic effect in the rat with chronic pain induced by nerve ligation (Obata et al., 2001). Intrathecal administration of a 5-$HT_{2A/2C}$ receptor agonist was shown to mediate antinociception in inflammatory pain, and neuropathic pain and this effect was reversed by ketanserin, indicating that 5-$HT_{2A/2C}$ receptors play a critical role in nociception (Obata et al., 2001). As in the present study, fluoxetine-induced antinociception was reversed by ritanserin but not by ondansetron.

In conclusion, this study clearly demonstrates that the role of 5-$HT_{1/2}$ receptors in the antinociceptive effect of fluoxetine in diabetic neuropathic pain. The findings also demonstrate the beneficial effect of combination of an antidepressant and 5-HT_{1A} receptor antagonist in the treatment of neuropathic pain. This combination may reduce the delay in the antinociceptive effect of antidepressants and increase their potency in painful diabetic neuropathy.

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