Korean J Physiol Pharmacol
Vol 2: 661–670, December, 1998

Dopaminergic Inhibition of Dorsal Horn Cell Activity in the Cat

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Dopamine has been generally known to exert antinociceptive action in behavioral pain test, such as tail flick and hot plate test, but there appears to be a great variance in the reports on the antinociceptive effect of dopamine depending on the dosage and route of drug administration and type of animal preparation. In the present study, the effects of dopamine on the responses of wide dynamic range (WDR) cells to mechanical, thermal and graded electrical stimuli were investigated, and the dopamine-induced changes in WDR cell responses were compared between animals with an intact spinal cord and the spinal animals. Spinal application of dopamine (1.3 & 2.6 mM) produced a dose-dependent inhibiton of WDR cell responses to afferent inputs, the pinch-induced or the C-fiber evoked responses being more strongly depressed than the brush-induced or the A-fiber evoked responses. The dopamine-induced inhibition was more pronounced in the spinal cat than in the cat with intact spinal cord. The responses of WDR cell to thermal stimulation were also strongly inhibited. Dopamine D_2 receptor antagonist, sulpiride, but not D_1 receptor antagonist, significantly blocked the inhibitory action of dopamine on the C-fiber and thermal responses of dorsal horn cells. These findings suggest that dopamine strongly suppresses the responses of WDR cells to afferent signals mainly through spinal dopamine D_2 receptors and that spinal dopaminergic processes are under the tonic inhibitory action of the descending supraspinal pathways.

Key Words: Dopamine, WDR cell activity, Spinal cat, Descending dopaminergic inhibition

INTRODUCTION

Dopamine in the spinal cord has been known to function as a precursor substance for norepinephrine synthesis, but experimental findings suggest that in the spinal cord, dopaminergic neurons exist independently of noradrenergic neurons. In the rat spinal cord, dopamine, dopaminergic neurons and dopamine receptors are highly concentrated in the dorsal horn (Hökfelt et al, 1979; Demenge et al, 1981; Gentleman et al, 1981; Skagerberg & Lindvall, 1985). After spinalization at the thoracic level, the dopamine concentration and dopamine-induced inhibitory action on the adenylate cyclase are known to decrease in the lumbar level of the experimental animals (Commissiong et al, 1978; Gentleman et al, 1981). These findings imply that there is a direct descending dopaminergic projection to the spinal cord from the brain area. Another evidence suggesting that dopamine and norepinephrine act as a separate neurotransmitter is that the dopamine concentration in the spinal cord does not change even after the bilateral destruction of locus coeruleus (Commissiong et al, 1978; Mouchet et al, 1982), which is the major source of noradrenergic innervation to the spinal cord, whereas the norepinephrine concentration in the spinal cord decreases greatly (Commissiong et al, 1978; Mouchet et al, 1982). If dopamine was a precursor substance for norepinephrine, it would clearly be reduced in parallel with norepinephrine.

It is generally accepted that dopamine and its agonists exert dose-dependent antinociceptive actions mediated through dopamine D_2 receptors in the behavioral test such as tail flick and hot plate test

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(Michael-Titus et al, 1990; Morgan & Franklin, 1991; Liu et al, 1992). However, there appears to be a great variance in the reports on the antinociceptive effect of dopamine agonists. Dopamine D_2 receptor agonists are reported to produce antinociceptive actions after i.c.v. administration but hyperalgesic effects following s.c. or i.p. administration (Ben-Sreti et al, 1983; Roane & Paul, 1991). It was also demonstrated that dopamine D_2 agonist (i.p.) at a low concentration elicits a hyperalgesic effect while at a high concentration an analgesic action (Paalzow & Paalzow, 1983; Kostrzewa et al, 1991). Jensen and his colleagues reported that the dopamine-induced antinociception was observed only in the spinal animals or in the animals with bilaterally lesioned dorsolateral funiculus (DLF) (Jensen & Smith, 1983a; Jensen & Smith, 1983b; Jensen et al, 1984).

Electrical stimulation of substantia nigra is known to produce an analgesia in behavioral pain test (Segal & Sandberg, 1977; Sandberg & Segal, 1978) and also to suppress the responses of laminar V cells to electrical stimulation of C- afferent nerve and to pinch applied to the receptive field (Barnes et al, 1979). These antinociceptive responses are antagonized by dopamine receptor blocker, bulbocapnine and serotonergic blocker, methysergide (Sandberg & Segal, 1978; Barnes et al, 1979). On the basis of these experimental findings, Barnes et al (1979) suggested that the activities of substantia nigra are relayed in part through the descending raphe system. Activation of the A11 area, another source of dopaminergic innervation, selectively inhibits the response of multireceptive neurons to noxious heat, which is antagonized by dopamine D_2 receptor antagonist, sulpiride, but not by D_1 receptor antagonist, SKF38393 (Fleetwood-Walker & Hope, 1985; Fleetwood-Walker et al, 1988). On the other hand, it was demonstrated that the activation of dopamine receptors inhibits analgesia produced by foot-shock (Tricklebank et al, 1984), vaginocervical stimulation (Cunningham & Komisaruk, 1995) and acupuncture (Zhu et al, 1995) whereas haloperidol significantly potentiates analgesic responses in the streptozotocin-induced diabetic rats (Rutledge et al, 1995).

Also, it was suggested that dopamine- and its agonist-induced inhibitory action is mediated through the reduction of intracellular Ca^{2+} mobilization, which results in the inhibition of transmitter release. Dufy et al (1979) reported that in prolactin secreting cells, the Ca^{2+}-dependent action potential was reduced by dopamine D_2 receptor agonist, RU24213. In striatal slices, apomorphine and LY-171555 also suppressed the elevation of intracellular calcium and the release of acetylcholine by depolarizing stimuli (Rutledge et al, 1995). However, depolarizing stimuli did not induce an increment in intracellular calcium level and in transmitter release in Ca^{2+} free medium. Sulpiride, but not SKF38393, antagonized these suppressive actions of apomorphine and LY-171555. Fujiwara et al (1987) emphasized the existence of a high correlation between D_2 receptor-mediated inhibition of intracellular calcium and transmitter release.

In the present study, we investigated the effects of dopamine on the responsiveness of wide dynamic range (WDR) cells to mechanical, thermal and graded electrical stimuli and placed an emphasis on the comparison of the dopamine-induced changes in the responses of WDR cells between the normal cat and the spinal cat. Also studied were the effect of D_1 and D_2 receptor antagonists on the dopamine-induced inhibition.

METHODS

Thirty one cats were anesthetized with intravenously administered α-chloralose (60 mg/kg) after tranquilizing with ketamine HCl (10 mg/kg, i.v.). Experimental animals were artificially ventilated, and the end-tidal CO_2 was maintained at 3.5 to 4.5%. The muscles were paralyzed with intravenous injection of pancuronium bromide (0.3 mg/kg/hr) throughout the entire experimental periods. The rectal temperature was kept near 37°C by homeothermic blanket system (Harvard Apparatus CO. Inc.). The experiment was terminated when mean arterial pressure fell below 80 mmHg.

The lumbosacral spinal cord was exposed by laminectomy at the L4-S1 level for recording single unit activity of dorsal horn neurons. The exposed spinal cords were transected at the T13 level in 21 of 31 cats. The common peroneal and tibial nerves were dissected free from surrounding connective tissues and placed on a tripolar platinum electrode for electrical stimulation. Liquid paraffin pools were made around the exposed spinal cord and peripheral nerves to prevent drying.

Single unit activity of dorsal horn neurons activited by the electrical stimulation of afferent nerves was recorded in the lumbar enlargement. The types of

dorsal horn neurons were classified according to the response pattern to mechanical stimuli (brush and pinch) applied to the receptive field. Only the WDR cells that responded both to A and C fiber input were used in this experiment. Brush and pinch stimuli were applied to the receptive field for 10 sec., respectively. The A or C fiber responses were compiled from 10 consecutive stimulations of afferent nerves with a single pulse (0.1 msec) or a train of three pulses (0.5 msec, 33 Hz or 50 Hz), respectively. The intensity of stimuli was adjusted to activate only A fibers (10T, T:times the threshold for activation of Aβ fibers) or all A and C fibers (200~300 T). And also applied were the thermal stimuli (40-44-48°C) to the receptive field for 20 sec, respectively. The electrical activity was amplified (WPI, DAM80), displayed on an oscilloscope and fed into a window discriminator (Frederic Haer and Co.) whose output was used by a computer to compile the poststimulus time histogram.

The responses of WDR cells to graded electrical stimulation of afferent nerves and thermal stimulation as well as mechanical stimulation of the receptive field were recorded before and after the spinal application of dopamine (1.3 mM & 2.6 mM) in the cat with an intact spinal cord and in the spinal cat as well. The spinal application is recognized to be equivalent to intrathecal administration which has been very widely used in behavioral pain test. And also studied were the effects of dopamine D_1 receptor antagonist, SCH23390 (0.5 mM), and D_2 receptor antagonist, sulpiride (3mM) on the dopamine-induced changes in the WDR cell responses.

Because the size of evoked responses varied from one unit to another, data were expressed as percentage of discharges in the control state. Statistical significance was determined by student's t test. P values less than 0.05 were considered significant.

RESULTS

Dopamine-induced inhibitions of WDR cell responses to mechanical stimuli were compared between the cat with an intact spinal cord (the normal cat) and the spinal cat whose spinal cord was crushed with fine forceps at T13 level. No significant inhibitions were observed in the responses of WDR

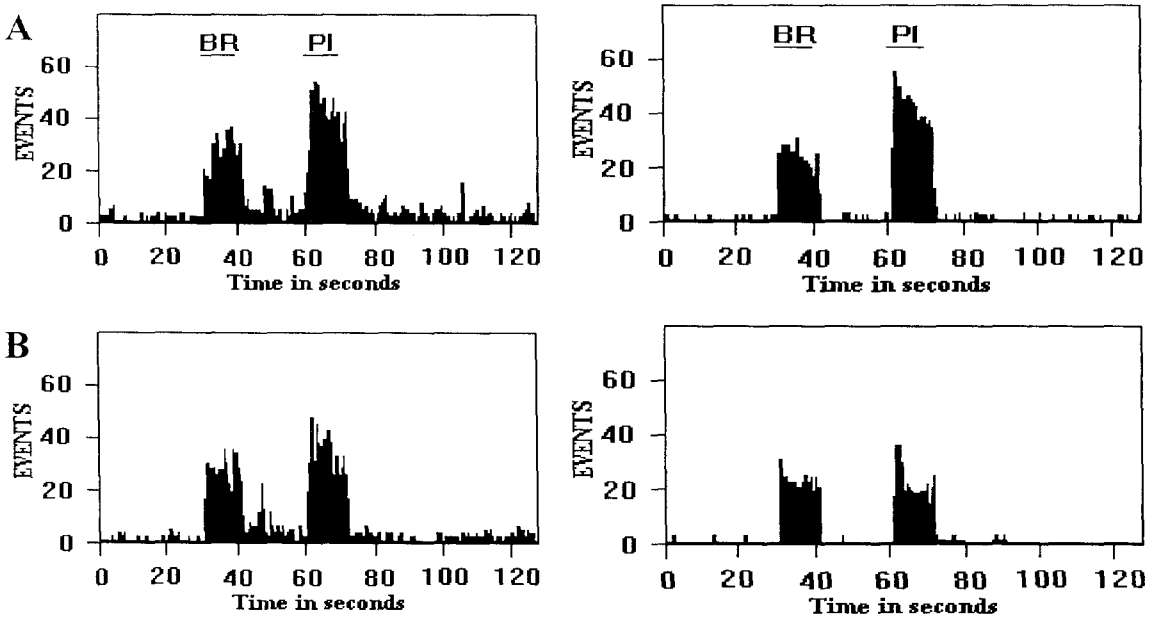

Fig. 1. The responses of WDR cells to the mechanical stimulations before (A & C) and after (B & D) the spinal application of dopamine (2.6 mM sol.) in the normal cat (A & B) and the spinal cat (C & D). BR: brush, PI: pinch. Each mechanical stimulus was applied to the receptive field for 10 sec. A & C: the control responses of WDR cells to brush and pinch. The responses of WDR cells to pinch were more strongly suppressed in the spinal cat (D) than in the cat with an intact spinal cord (B) after the spinal application of dopamine.

cells to brush stimulus in both the normal (N=8) and spinal (N=9) cat in 30 min after the spinal application of 2.6 mM dopamine (Fig. 1). However, in both the normal and spinal cat, the responses to pinch were significantly suppressed to 80.8±6.2% ($p<0.02$) and 54.5±6.5% ($P<0.01$) of the control, respectively, the response in the spinal cat being more strongly inhibited (Fig. 1).

Also studied were the effects of dopamine on the A- and C-fiber responses of WDR cells to the graded electrical stimulation of afferent nerve. At the dose of 2.6 mM, the A-fiber responses were reduced to 81.8±9.3% (Fig. 2A2) and 84.6±5.1% (Fig. 3A3) ($P<0.05$) of the control both in the normal and spinal cat, respectively. Dopamine suppressed the C-fiber responses more strongly than the A-fiber ones (Fig. 2B2 & 3B3). Its inhibitory action was dose-dependent and more stronger in the spinal cat than in the normal cat. The C-fiber responses were inhibited to 33.2± 9.0% in the spinal cat (N=12) (Fig. 3B3) and 60.6± 10.2% (Fig. 2B2) in the normal cat (N=7).

Fig. 4 summarizes the inhibitory action of dopamine on the pinch and the C-fiber responses in the spinal and normal cats. As the inhibitory action of dopamine was more prominent in the spinal cat, the following experiments were carried out in the spinal cat.

As shown in Fig. 5, the responses of WDR cells to thermal stimuli (40-44-48°C) were also suppressed to 22.9~32.1% of the control responses after the spinal application of 2.6 mM dopamine, but no relation was found between inhibitory action of

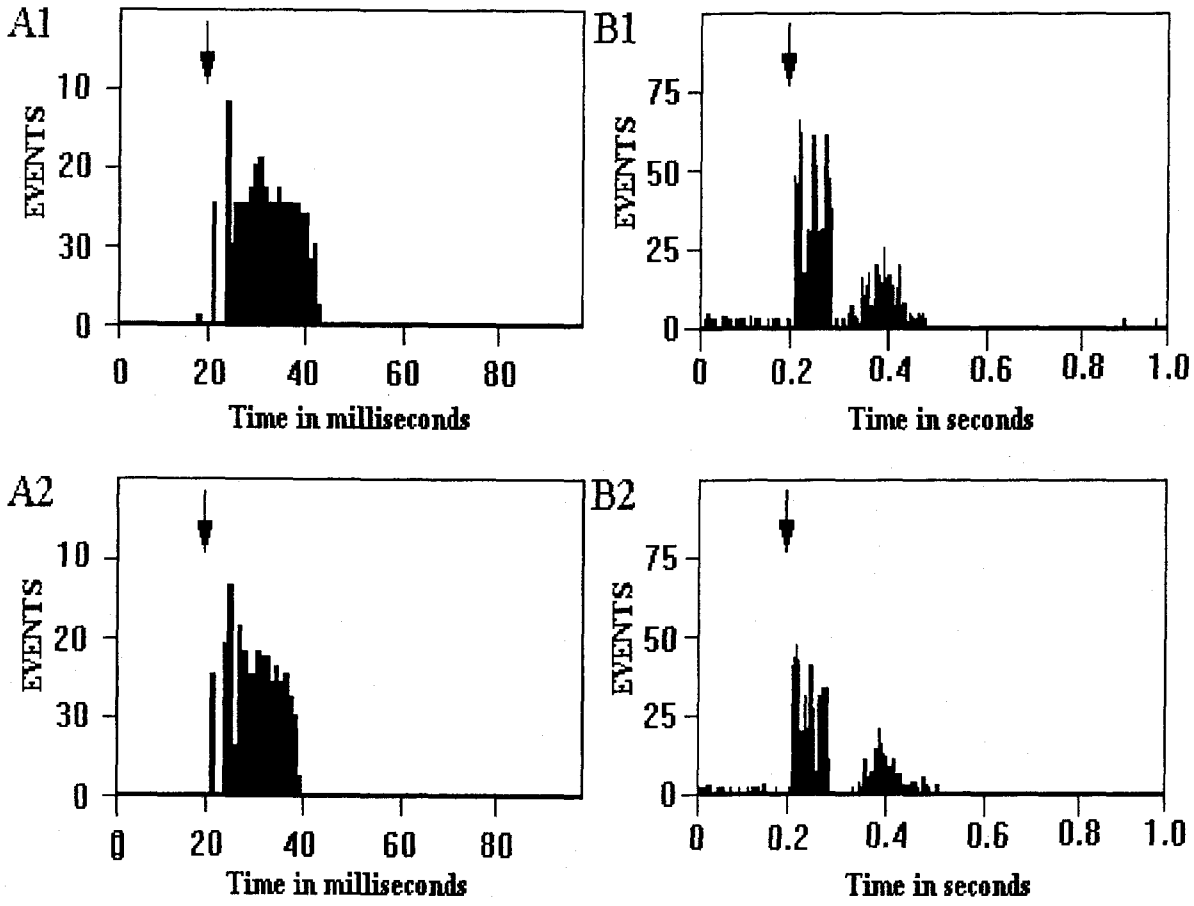

Fig. 2. Changes in the responses of WDR cells to the graded electrical stimulation of afferent nerve following the spinal application of dopamine (2.6 mM) in the normal cat. Arrows indicate the time at which single (A) or 3 train stimuli (B) were applied to afferent nerve. A1 & B1: the control A-(A1) and C-fiber (B1) responses of WDR cells to graded electrical stimulation of afferent nerve. After the spinal application of dopamine, C-fiber responses of WDR cells (B2) were more strongly inhibited than A-fiber responses (A2).

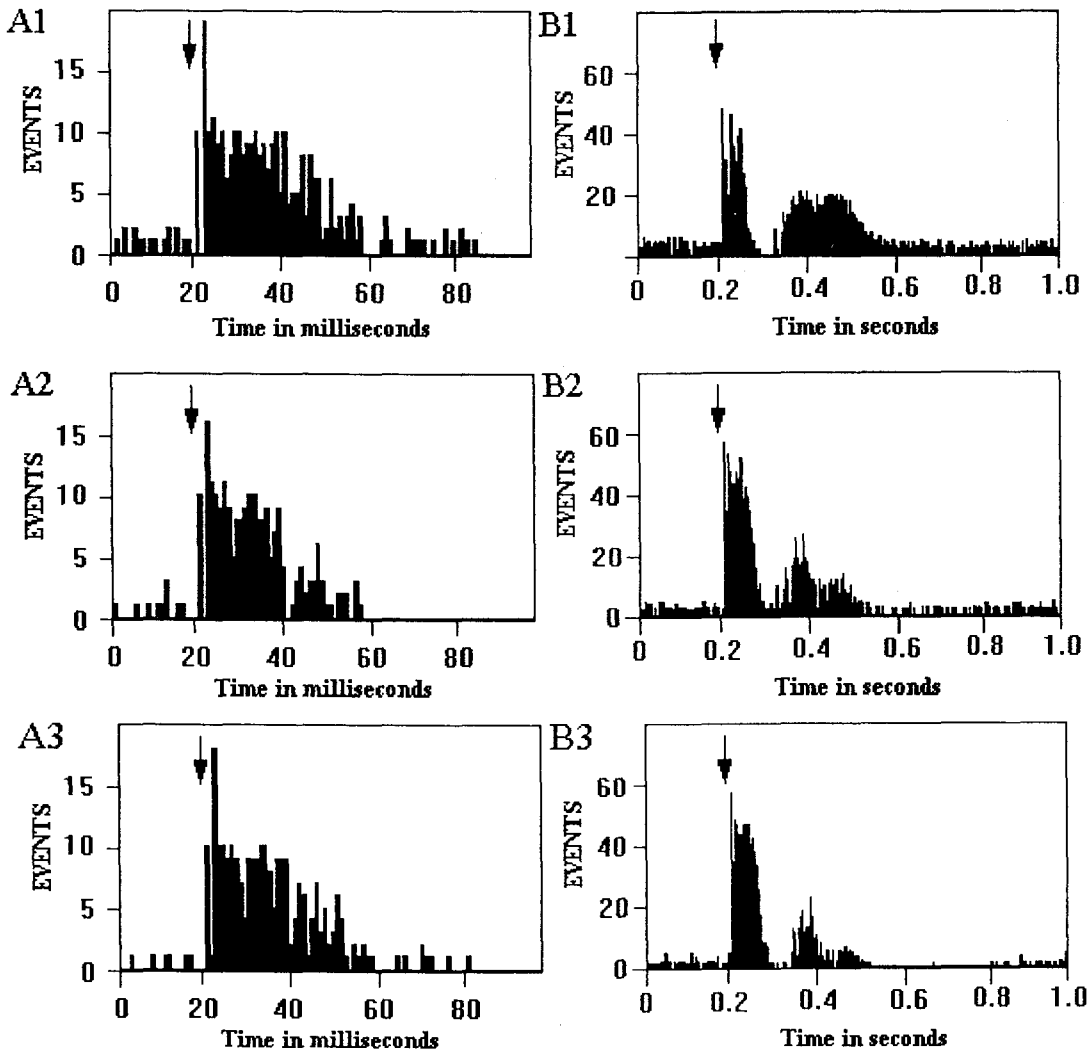

Fig. 3. Inhibitory action of dopamine on the responses of WDR cells to graded electrical stimulation of afferent nerve in the spinal cat. Arrows indicate the time at which single (A) or 3 train stimuli (B) were applied to afferent nerve. A1 & B1: the control A-(A1) and C-fiber (B1) responses of WDR cells to graded electrical stimulation of afferent nerve. Dopamine (1.3 mM & 2.6 mM) depressed C-fiber responses in a dose-dependent manner (B2 & B3) while it had very weak inhibitory action on A-fiber responses (A2 & A3).

dopamine and intensity of thermal stimuli. Therefore, changes in WDR cell response only to the thermal stimulation of 44°C were described. 2.6 mM dopamine suppressed WDR cell response to the 44°C thermal stimulation to 29.3±5.4% of the control (N=8). After the spinal application of sulpiride, the suppressed response to thermal stimulation recovered to 57.1±7.6% of the control, suggesting that inhibitory action of dopamine was significantly antagonized by sulpiride. However, the dopamine-induced inhibitory action of WDR cell response to thermal stimulation was not altered even after spinal application of dopamine D_1 receptor antagonist, SCH23390 (Fig. 5 & Fig. 7).

The responses of WDR cell to C-fiber stimulation were strongly suppressed to 33.2±9.0% of the control by the spinal application of 2.6 mM dopamine (N=9). This suppressed response of WDR cell to C-fiber stimulation recovered to 97.9±10.3% of the control after the spinal application of sulpiride, but not of SCH23390 (Fig. 6 & Fig. 7).

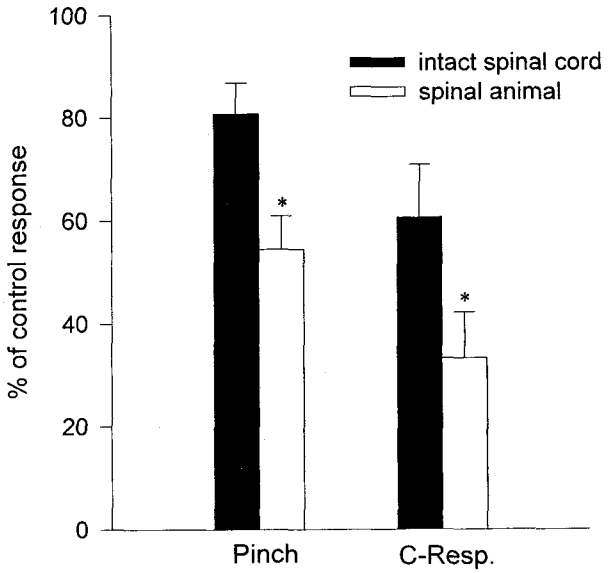

Fig. 4. Comparision of the changes in dopamine-induced inhibition of WDR cell responses to pinch and C-fiber stimulation recorded in the spinal cat and the normal cat. The responses to pinch and C-fiber simulation were more strongly inhibited by dopamine (2.6 mM) in the spinal cat than in the normal cat. Each value represents the mean±S.E. *: sigmificant differences from the responses recorded in the normal cat.

DISCUSSION

Many studies on the effects of dopamine and its agonists reported that dopamine agonists have antinociceptive actions on acute and tonic pains caused mainly in behavioral tests, such as tail flick, hot plate, and formalin tests (Michael-Titus et al, 1990; Morgan & Franklin, 1991; Liu et al, 1992). Also electrical stimulation of dopaminergic neurons in the diencephalon is known to inhibit the responses of dorsal horn neurons to noxious stimuli without any effect on the responses to innocuous stimuli (Segal & Sandberg, 1977; Barnes et al, 1979; Fleetwood-Walker et al, 1988).

However, dopaminergic effects on nociceptive processes appear to be very variable depending on the dosage and route of drug administration (Ben-Sreti et al, 1983; Paalzow & Paalzow, 1983; Kostrzewa et al, 1991; Roane & Paul, 1991) and animal preparation (Jensen & Smith, 1983a; Jensen & Smith, 1983b; Jensen et al, 1984). In the present study, direct spinal application of dopamine strongly suppressed the responses of WDR cells to noxious stimuli such as pinching, electrical stimulation of C-afferent fibers, and thermal stimulation of the receptive field. However, dopamine had the least effects on the responses to innocuous stimuli, such as A-fiber stimulation and brushing.

The present finding that dopamine selectively inhibited the nociceptive responses in the cat spinal cord agrees well with known antinociceptive action of dopamine on the acute and tonic pain in behavioral test (Michael-Titus et al, 1990; Morgan & Franklin, 1991; Liu et al, 1992) and extends the results of Fleetwood-Walker et al (1988) that dopamine selectively inhibited the responses of dorsal horn neurons to noxious heat and pinch without any effect on the responses to innocuous stimuli. We confirmed for the first time that of the responses induced by three noxious stimuli, the responses of WDR cells to C-fiber stimulation as well as thermal stimuli were most strongly inhibited by the spinal application of dopamine.

Another feature of this study is that dopamine produced stronger inhibitory action on the WDR cell responses in the spinal cat than in the normal cat with an intact spinal cord. Jensen and his colleagues reported that intrathecally administered apomorphine did not have any inhibitory effects on tail flick latency in the rat with an intact spinal cord. They observed a dose-dependent analgesic action of apomorphine only in the rat whose spinal cord or bilateral DLF had been transected at thoracic level (Jensen & Smith, 1983a; Jensen & Smith, 1983b; Jensen et al, 1984). After the pretreatment with methysergide and/or phentolamine, the dose-dependent antinociceptive action of apomorphine was observed even in the rat with an intact spinal cord (Jensen & Smith, 1983a). On the basis of these experimental findings, Jensen & Smith (1983a, b) reached a conclusion that spinal dopaminergic mechanism was under the tonic inhibitory action of serotonergic and/or noradrenergic descending system, which was transmitted through DLF to spinal cord. A greater inhibitory action of dopamine that we observed in the spinal cat seems to result from the disinhibition of descending supraspinal inhibition.

Dopamine receptors were originally classified into two main types, according to whether or not they were linked to activation of adenylate cyclase (Kebabian & Calne, 1979). Stimulation of D_1 receptors activates adenylate cyclase and stimulation of D_2 receptors inhibits or does not stimulate the activity of

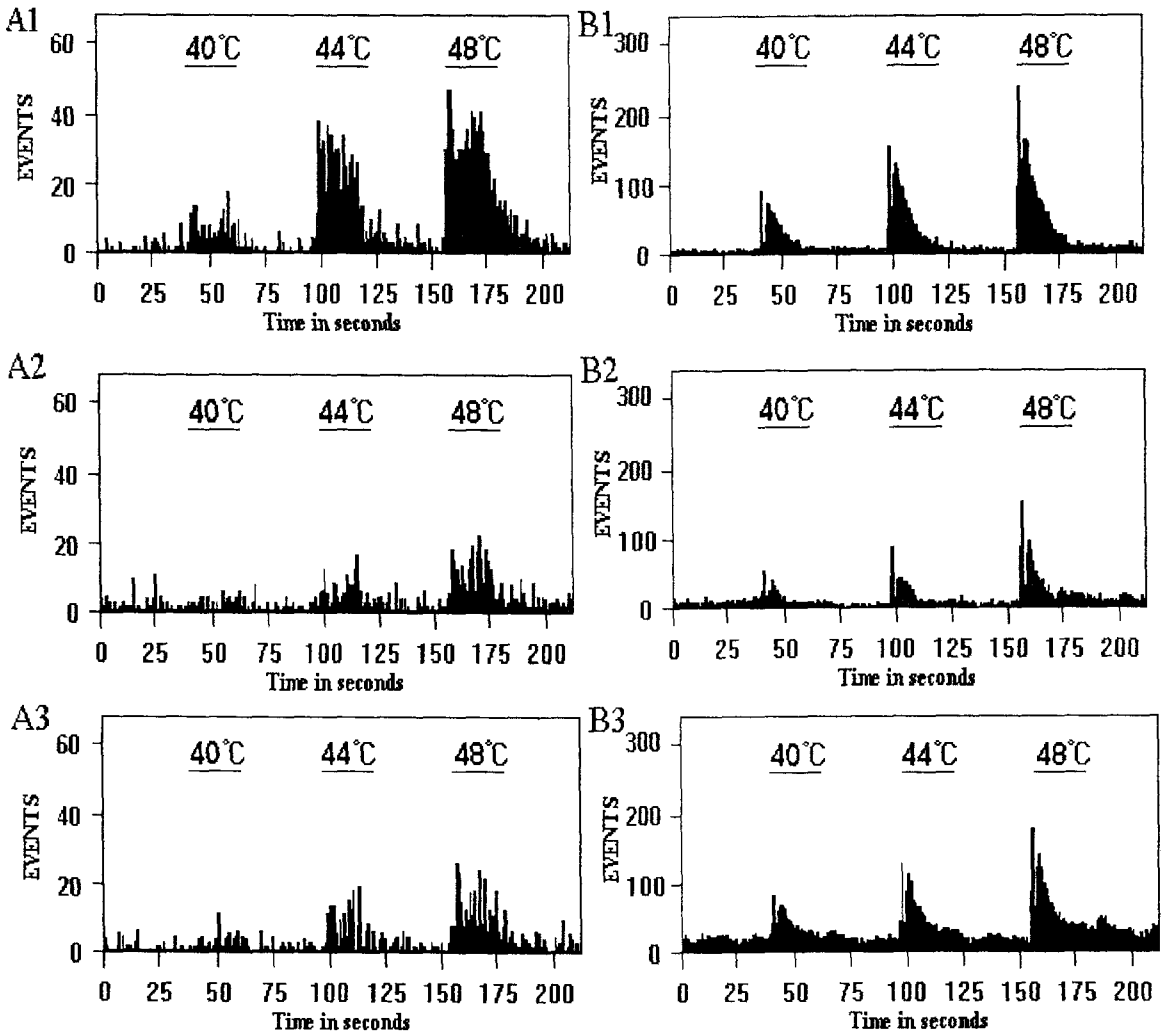

Fig. 5. Changes in the inhibitory effects of dopamine (2.6 mM) on the thermal responses of WDR cells before and after the spinal application of dopamine antagonists. A1 & B1 : the control responses of WDR cell to graded thermal stimulation (40°C-44°C-48°C). Thermal responses of WDR cell were greatly inhibited after the spinal application of dopamine (A2 & B2). A3 & B3: the spinal application of sulpiride weakly but significantly antagonized the inhibitory action of dopamine (B3) while dopamine- induced inhibition was not changed after the spinal application of SCH23390 (A3)

this enzyme (Kebabian et al, 1984). The two main receptors (D_1 & D_2) were further subdivided into the five subtypes (D_1-D_5) which are also known to have many variants (Grandy et al, 1991; Van Tol et al, 1992; Schmauss et al, 1993; Seeman & Van Tol, 1994). In this study, antagonists of two typical types of dopamine receptors were used to find the type of receptor which mediated inhibitory action of dopamine on the responses of WDR cells in the spinal cord. Dopamine D_2 receptor antagonist, sulpiride, but not D_1 receptor antagonist, strongly antagonized inhibitory action of dopamine on the responses of WDR cells to thermal stimulation of the receptive field and to electrical stimulation of afferent nerve. This result suggests that the dopamine-induced inhibition was mediated through spinal dopamine D_2 receptors, which is in accord with the results of other investigators that dopaminergic receptors are highly concentrated in the dorsal horn (Demenge et al, 1981; Gentleman et al, 1981) and that dopamine D_2 receptor antagonists blocked dopamine- and its agonist-induced antinociceptive actions in the behavioral pain tests (Michael-Titus et al, 1990; Morgan & Franklin, 1991; Liu et al, 1992). However, dopamine in the

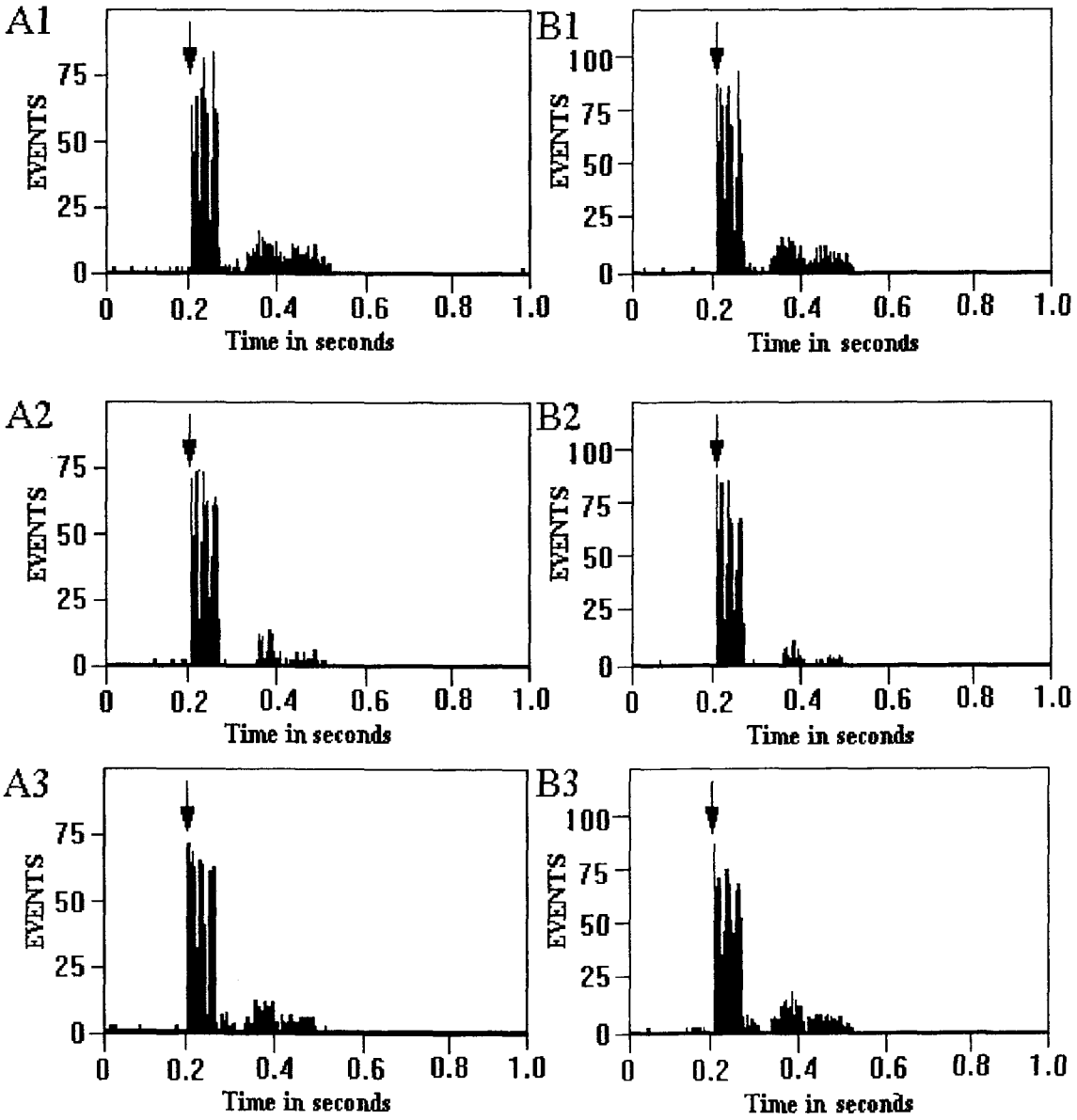

Fig. 6. Changes in the inhibitory effects of dopamine (2.6 mM) on the responses of WDR cells to graded electrical stimulation of the afferent nerve before and after the spinal application of dopamine antagonists. Arrows indicate the time at which 3 train stimuli were applied to afferent nerve. A1 & B1: the control C-fiber responses to electrical stimulation of common peroneal nerve. Dopamine had strong inhibitory action on C-fiber responses (A2 & B2) which was antagonized by the spinal application of sulpiride (B3) but not by spinal SCH23390 (A3).

spinal cord does not seem to have tonic inhibitory action because dopamine antagonist by itself never causes any changes in the basal tail flick latency (Morgan & Franklin, 1991; Liu et al, 1992).

The dopamine-induced inhibitory action probably has a close relationship with changes in intracellular Ca^{2+} concentration and membrane excitability. Apomorphine and amphetamine reduce the excitability and firing rate of nigro-striatal dopaminergic neurons whereas dopamine receptor antagonists, such as haloperidole, sulpiride and fluphenazine increased the excitability (Aghajanian & Bunney, 1977; Groves et al, 1981; Tepper et al, 1984). Tepper et al (1984) suggested that dopaminergic inhibitory action on nigro-striatal neurons were associated with dopamine autoreceptor-mediated hyperpolarization and/or alter-

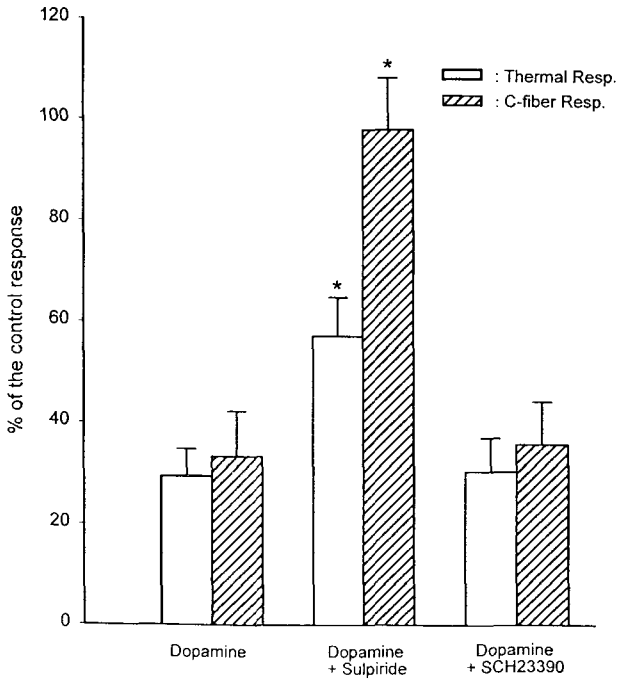

Fig. 7. Changes in the dopamine-induced inhibition of WDR cell responses to thermal and C-fiber stimulation after single or combined application of dopamine, sulpiride and SCH23390 in the spinal cat. *: significant differences from the dopamine-induced inhibition of WDR cell response.

ation in ionic conductance of the terminal membrane. It was well documented that dopamine agonists inhibit the Ca^{2+}-dependent action potential (Dufy et al, 1979) and also the increase in the intracellular Ca^{2+} level induced by electrical stimulation or high K^+ (Fujiwara et al, 1987), which are antagonized by a dopamine D_2 receptor antagonist, sulpiride, but not by a D_1 receptor antagonist, SKF38393 (Fujiwara et al, 1987). Fujiwara et al (1987) found that in neostriatal neurons, there was a high correlation between the D_2 receptor-mediated inhibiton of intracellular Ca^{2+} level and transmitter release. In fact, there are a few studies which demonstrated employing microdialysis technique that dopamine D_2 receptor agonists inhibit, but D_2 receptor antagonists increase acetylcholine release from the striatal neurons (Bertorelli & Consolo, 1990; De Boer et al, 1992; Imperato et al, 1994). Putting all these available informations together, we conclude that the dopamine D_2 receptor-mediated inhibition observed in the present study may be due to an inhibition of intracellular Ca^{2+} mobilization and to descrease in the membrane excitability.

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