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Modulation of [^{3}H]dopamine release by neuropeptide Y in rat striatal slices

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Abstract

Neuropeptide Y, a 36-amino-acid peptide, has a wide and specific distribution in the central nervous system. In this study we examined the regulatory mechanisms of neuropeptide Y on dopamine release in the rat central nervous system. The effects of neuropeptide Y on the electrically stimulated [^{3}H]dopamine release were investigated in superfused striatal slices of Sprague-Dawley rats, spontaneously hypertensive rats and Wistar-Kyoto rats. Neuropeptide Y (1×10^{-8}–1×10^{-7} mol/l) reduced the stimulation (1 Hz)-induced [^{3}H]dopamine release by a comparable amount in Sprague-Dawley rats. The blockade of dopamine D_2 receptors by the dopamine D_2 receptor antagonist, sulpiride, diminished the inhibitory effects of neuropeptide Y on the stimulation-evoked [^{3}H]dopamine release. Pretreatment of slices with pertussis toxin (a potent inhibitor of G_i-proteins) attenuated the suppression of the stimulation-evoked [^{3}H]dopamine release by neuropeptide Y. Unlabelled dopamine itself reduced the stimulation-evoked [^{3}H]dopamine release, and the inhibitory effect was also attenuated in the pertussis toxin-pretreated slices. In spontaneously hypertensive rats, the inhibitory effect of neuropeptide Y on the stimulation-evoked [^{3}H]dopamine release was more pronounced than that in Wistar-Kyoto rats. The results of the present study showed that neuropeptide Y inhibited the stimulation-evoked dopamine release partially mediated by dopamine D_2 receptors and the pertussis toxin-sensitive G_i-proteins in rat striatum. Furthermore, the greater effect of neuropeptide Y on dopamine release in spontaneously hypertensive rats suggests a possible involvement of the peptide in regulating the central dopaminergic nerve activity in hypertension.

Keywords: Neuropeptide Y: Dopamine release; Dopamine D_2 receptor; G_i-protein; Striatum; Spontaneously hypertensive rat (SHR)

1. Introduction

Neuropeptide Y is a 36-amino-acid peptide, and has a wide and specific distribution in both the central and peripheral nervous systems (Tatemoto et al., 1982; Everitt et al., 1984). Consistent with the distribution of neuropeptide Y, many physiological functions are modulated by the peptide. These include regulations of the cardiovascular functions, neural activities and sympathetic neurotransmission (Michel and Rascher, 1995). In peripheral tissues such as rat portal vein, it was observed that neuropeptide Y had a presynaptic effect and inhibited the stimulation-evoked norepinephrine release (Dahlöf et al., 1985). In the central nervous system, we showed that neuropeptide Y reduced the stimulation-evoked norepinephrine release in the hypothalamus of normotensive and spontaneously hypertensive rats (SHR) (Tsuda et al., 1989, 1990).

Anatomical studies have described that the neuropeptide Y-immunoreactive axons and terminals are distributed in the striatum (Aoki and Pickel, 1990). Vuillet et al. (1989a,b) showed that nigrostriatal dopamine nerve endings contact neuropeptide Y-containing neurons in rat striatum. It was also demonstrated that in an in vivo study the central administration of neuropeptide Y modulated the turnover of dopamine in the striatum (Beal et al., 1986; Heilig et al., 1990; Vallejo et al., 1987). These previous findings raise the possibility that neuropeptide Y may interact with the dopaminergic systems, although the possible mechanisms of the functional relationship are not clear yet.

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Recently, the involvement of central dopaminergic systems in the regulation of blood pressure has been described in both experimental and human hypertension. Kolloch et al. (1980) reported that bromocriptine (the dopamine D_2 receptor agonist) significantly reduced the blood pressure in patients with essential hypertension, which suggested the significance of dopamine as an important depressor component in the central nervous system. Chiu et al. (1982) observed that [^{3}H]spiroperidol (the dopamine D_2 receptor antagonist) binding was significantly increased in the striatum of SHR compared with normotensive rats, and proposed that an abnormality in the striatal dopaminergic systems might have a role in the pathogenesis of hypertension.

It is well known that dopamine D_2 receptors in the striatum are negatively linked to adenylate cyclase by the inhibitory guanosine triphosphate binding proteins (G_i-proteins) (Ohara et al., 1988). Furthermore, it has been reported that the inactivation of the G_i-proteins by pertussis toxin impairs receptor-mediated regulation of adenylate cyclase as well as cellular responses caused by activation of the receptors (Murayama and Ui, 1983).

In the present study we investigated the influences of neuropeptide Y on the electrically evoked [^{3}H]dopamine release in rat striatum where dopaminergic fibers and their terminals exist in abundance, and further examined the effects of the dopamine D_2 receptor antagonist as well as the effects of inactivation of the G_i-proteins by pertussis toxin on the modulation of dopamine release in this region. Additionally, to test the possibility of abnormal presynaptic regulation of central dopamine release in hypertension, we evaluated whether neuropeptide Y-mediated regulation of dopamine release might be altered in the striatum of SHR.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats weighing 200–250 g (Taconic Farms, Germantown, NY, USA) were used for the investigation of the effects of neuropeptide Y in rat striatum. We also studied male SHR (8–10 weeks old, Taconic Farms), and compared with age-matched male Wistar-Kyoto (WKY) rats (Taconic Farms). The body weight of the SHR was 225.6 ± 6.5 g (mean $\pm$ S.E.M., $n = 6$) and that of WKY rats was 269.7 ± 15.1 g ($n = 6$). Systolic blood pressure, which was measured by the tail-cuff method (programmed electro-sphygmomanometer, model PE-300, Narco Biosystem, Houston, TX, USA), was 173.2 ± 6.8 mmHg in SHR ($n = 6$) and 116.8 ± 5.7 mmHg in WKY rats ($n = 6$). All rats were maintained and housed in a temperature-controlled and humidity-controlled room. The rats were fed regular pellet food and tap water ad libitum beginning at least 1 week before the experiment.

2.2. Drugs

The dopamine D_2 receptor antagonist, sulpiride, was obtained from Sigma Chemical Company (St. Louis, MO, USA). Neuropeptide Y was donated by D. Schlesinger (Cell Biology and Stanley H. Kaplan Cancer Center, New York University Medical Center, New York, NY, USA). Purified pertussis toxin was purchased from List Biological Laboratories (Campbell, CA, USA). All other drugs used were standard laboratory reagents of analytical grade.

2.3. Experimental procedures

The rats were decapitated, and the whole striatum was rapidly dissected on ice according to a method described previously (Lehmann et al., 1983; Versteeg and Ulenkate, 1987; Yokoo et al., 1988; Linthorst et al., 1990). The isolated striatum was sliced at 0.3 mm thickness by means of a tissue chopper (Brinkman Instrumental, Westbury, NY, USA). The sliced tissues were washed three times with 2 ml of Krebs-Ringer bicarbonate buffer (mmol/l: NaCl 118.0, KCl 4.80, $CaCl_2$ 1.20, KH_2PO_4 1.15, $MgSO_4$ 1.20, $NaHCO_3$ 25.0, glucose 11.1, ascorbic acid 0.11, and disodium EDTA 0.04, saturated with a mixture of 95% O_2 and 5% CO_2 at 37°C, pH 7.4). The slices were incubated with 3 ml of fresh buffer containing 0.1 μmol/l of [^{3}H]dopamine (specific activity 1.369×10^{12} Bq/mmol, New England Nuclear Research Products, Boston, MA, USA) for 20 min at 37°C. When striatal slices are incubated with [^{3}H]dopamine, the neurotransmitter stores of dopaminergic neurons are selectively labelled via the high-affinity uptake system for dopamine (Lehmann et al., 1983).

After the slices (5–7 mg) were rinsed with fresh buffer, they were transferred to a superfusion chamber (200 μl), jacketed with 37°C water, and suspended between two platinum electrodes (25 mm apart, 2.0 mm long). The slices were continuously superfused with Krebs-Ringer bicarbonate buffer at a rate of 0.7 ml/min. The superfusate was collected after 60 min of superfusion when basal release of tritium had stabilized to a constant level. Samples of superfusate were collected at 7-min intervals until the end of the experiment (at 130 min). For electrical stimulation, trains of unipolar rectangular pulses (1 Hz, 20 mA, 2 ms duration for 2 min) were delivered by using a Grass stimulator (model S4K, Grass Instrument, Quincy, MA, USA). Because the frequency of 1 Hz was characterized as the optimal stimulation frequency for investigating the actions of dopamine receptor agonists on electrically evoked [^{3}H]dopamine release (Lehmann et al., 1983), we have employed the stimulation frequency at 1 Hz in this study. The first period of electrical stimulation (S1) was

applied at 67 min, and the second period of electrical stimulation (S2) was applied at 116 min after the beginning of the superfusion. At the end of the experiment, the slices were solubilized by sonication for 20 s. Radioactivity in the collected samples and solubilized tissues was determined by liquid scintillation spectrometry (Tricarb Liquid Scintillation Spectrometer, model 3255, Packard Instrument, Sterling, VA, USA).

The amount of tritium released in each sample was calculated by dividing the total tritium collected in each sample by the total tritium present in the tissue at the time of the sample collection (the tritium released into superfusate after that point plus the tritium remaining in the tissue at the end of the experiment) and was expressed as percent fractional release. Basal release during the two prestimulation periods (b1 and b2, respectively) was evaluated from the tritium collected in the two 7-min prestimulation periods from the values in the stimulation periods, which included 2 min during stimulation plus 5 min after stimulation (7 min total).

We examined the effects of neuropeptide Y alone, and in combination with sulpiride and pertussis toxin on the [^{3}H]dopamine release in Sprague-Dawley rats. In pertussis toxin-treated slices, the effects of unlabelled dopamine on the stimulation-evoked [^{3}H]dopamine release were also studied. In the control experiment, S1 and S2 were performed in the absence of any added drugs. The effects of neuropeptide Y and unlabelled dopamine were evaluated only in S2 with S1 serving as an internal control. Superfusion with neuropeptide Y or unlabelled dopamine was initiated 14 min before S2 and maintained until the end of the experiment. The effects of neuropeptide Y and unlabelled dopamine on the stimulation-evoked [^{3}H]dopamine release were determined by comparing the S2/S1 ratios obtained in control slices with the values in slices treated with the agents in S2.

To examine the effects of blockade of dopamine D_2 receptors, sulpiride (1×10^{-6} mol/l) was added to the superfusion medium 28 min before S1 and maintained until the end of the experiment.

To inactivate the G_i-proteins, the slices of the striatum were preincubated for 1 h at 37°C in an atmosphere of 95% O_2 and 5% CO_2 in a mixture of 1380 μl of Krebs-Ringer bicarbonate buffer and 120 μl of sodium phosphate buffer (0.01 mol/l) that contained 0.05 mol/l of sodium chloride and 12 μg of pertussis toxin (concentration of 8 μg/ml). In the control experiment, the slices were incubated in the same buffer mixture without pertussis toxin. Subsequently, the slices were washed three times with fresh buffer and incubated in the presence of 0.1 μmol/l of [^{3}H]dopamine for 20 min at 37°C as previously described, and the effects of neuropeptide Y and unlabelled dopamine on the stimulation-evoked [^{3}H]dopamine release were determined.

In the next series of the experiment, the effects of neuropeptide Y on the stimulation-evoked [^{3}H]dopamine release were studied in the striatum of SHR compared with age-matched WKY rats.

2.4. Statistical analysis

Data are presented as means ± S.E.M. Differences between the means of the drug treatment and their corresponding controls were tested by a one-way analysis of variance (ANOVA). To compare the means of the different study groups, we used the Mann-Whitney *U*-test. To examine the differences between SHR and WKY rats, the two-way ANOVA was used. A P value less than 0.05 was accepted as the level of significance.

3. Results

3.1. Effects of neuropeptide Y alone and in combination with sulpiride on [^{3}H]dopamine release in the striatum of Sprague-Dawley rats

The tritium content of the first fraction collected ranged consistently around ≈ 9000 dpm and the tritium remaining in the tissue ranged around ≈ 160 000 dpm. In the control experiment, the stimulation-evoked [^{3}H]dopamine release in each of the two consecutive periods was 1.887 ± 0.060% of total tissue radioactivity ($n = 6$) during S1 and 1.544 ± 0.052% of total tissue radioactivity ($n = 6$) during S2, respectively (S2/S1 ratio, 0.818 ± 0.020, $n = 6$).

Table 1 demonstrates the effects of neuropeptide Y on [^{3}H]dopamine release in rat striatal slices. Neuropeptide Y (1×10^{-8}–1×10^{-7} mol/l) inhibited the stimulation-evoked [^{3}H]dopamine release by a comparable amount, although the basal release of [^{3}H]dopamine was not significantly affected by the peptide.

In a separate experiment, we studied the effects of sulpiride (the dopamine D_2 receptor antagonist) on the neuropeptide Y-induced reduction in [^{3}H]dopamine release. The absolute value of the fractional release during the stimulation-evoked [^{3}H]dopamine release was increased in the presence of sulpiride (Table 1). It is clearly demonstrated that exposure of slices to sulpiride significantly attenuated the inhibitory potency of neuropeptide Y on the stimulation-evoked [^{3}H]dopamine release (Table 1).

3.2. Effects of neuropeptide Y and unlabelled dopamine on the stimulation-evoked [^{3}H]dopamine release in pertussis toxin-treated striatal slices of Sprague-Dawley rats

The stimulation-evoked [^{3}H]dopamine release was not altered by the treatment with pertussis toxin (fractional release during S1 in control experiment 1.936 ± 0.054% of total tissue radioactivity, $n = 6$, fractional release during S2 in control experiment 1.720 ± 0.117% of total tissue radioactivity, $n = 6$, S2/S1 ratio 0.883 ± 0.042, $n = 6$).

Fig. 1 shows the effects of neuropeptide Y and unla-

Table 1
Effects of neuropeptide Y (NPY) on the stimulation-evoked and basal release of [^{3}H]dopamine in striatal slices of Sprague-Dawley rats

	Fractional release (%)		Ratio	Fractional release (%)		Ratio
	S1	S2	S2/S1	b1	b2	b2/b1
Control ($n = 6$)	1.887 ± 0.060	1.554 ± 0.052	0.818 ± 0.020	5.698 ± 0.151	4.792 ± 0.136	0.842 ± 0.021
NPY 1×10^{-8} mol/l ($n = 6$)	1.852 ± 0.068	1.014 ± 0.107 [a]	0.554 ± 0.048 [a]	5.811 ± 0.118	5.008 ± 0.110	0.861 ± 0.012
NPY 1×10^{-7} mol/l ($n = 6$)	1.769 ± 0.058	0.843 ± 0.065 [a]	0.478 ± 0.033 [a]	5.914 ± 0.172	4.856 ± 0.207	0.818 ± 0.011
In the presence of 1×10^{-6} M sulpiride						
Control ($n = 6$)	3.787 ± 0.153	2.916 ± 0.171	0.770 ± 0.033	5.718 ± 0.210	4.812 ± 0.172	0.841 ± 0.009
NPY 1×10^{-8} mol/l ($n = 6$)	3.616 ± 0.201	2.577 ± 0.147	0.714 ± 0.013 [c]	5.895 ± 0.186	5.174 ± 0.167	0.876 ± 0.007
NPY 1×10^{-7} mol/l ($n = 6$)	3.543 ± 0.156	2.215 ± 0.076 [b]	0.628 ± 0.018 [b,c]	5.856 ± 0.228	5.184 ± 0.253	0.885 ± 0.025

Values are represented as means ± S.E.M. Slices were stimulated twice (S1 and S2) at 1 Hz (20 mA, unipolar rectangular pulses of 2-ms duration for 2 min). Neuropeptide Y was added 14 min before S2. Fractional release at S1 and S2 was calculated by subtracting basal release (b1 and b2) from total release of tritium during stimulation period (2-min stimulation and after 5 min) and is expressed as percentage of the tritium content of the tissue at the onset of stimulation. Effects of neuropeptide Y on the stimulation-evoked and basal release of [^{3}H]dopamine were expressed as S2/S1 and b2/b1 ratios, respectively. [a] $P < 0.05$ compared with the corresponding control value. [b] $P < 0.05$ compared with the corresponding control value in the experiments when dopamine D_2 receptors were blocked by adding sulpiride (1×10^{-6} mol/l) at 28 min before S1. [c] $P < 0.05$ compared with the experiments in the presence of the same concentrations of neuropeptide Y alone.

belled dopamine on the stimulation-evoked [^{3}H]dopamine release in the pertussis toxin-treated slices. Pertussis toxin pretreatment significantly attenuated the suppression of [^{3}H]dopamine release by neuropeptide Y (S2/S1 ratio: control with pertussis toxin 0.883 ± 0.042, $n = 6$, control without pertussis toxin 0.832 ± 0.022, $n = 6$, neuropeptide Y 1×10^{-8} mol/l with pertussis toxin 0.819 ± 0.021, $n = 6$, neuropeptide Y1 $\times 10^{-8}$ mol/l without pertussis toxin 0.575 ± 0.051, $n = 6$, $P < 0.05$; neuropeptide Y 1×10^{-7} mol/l with pertussis toxin 0.757 ± 0.039, $n = 6$,

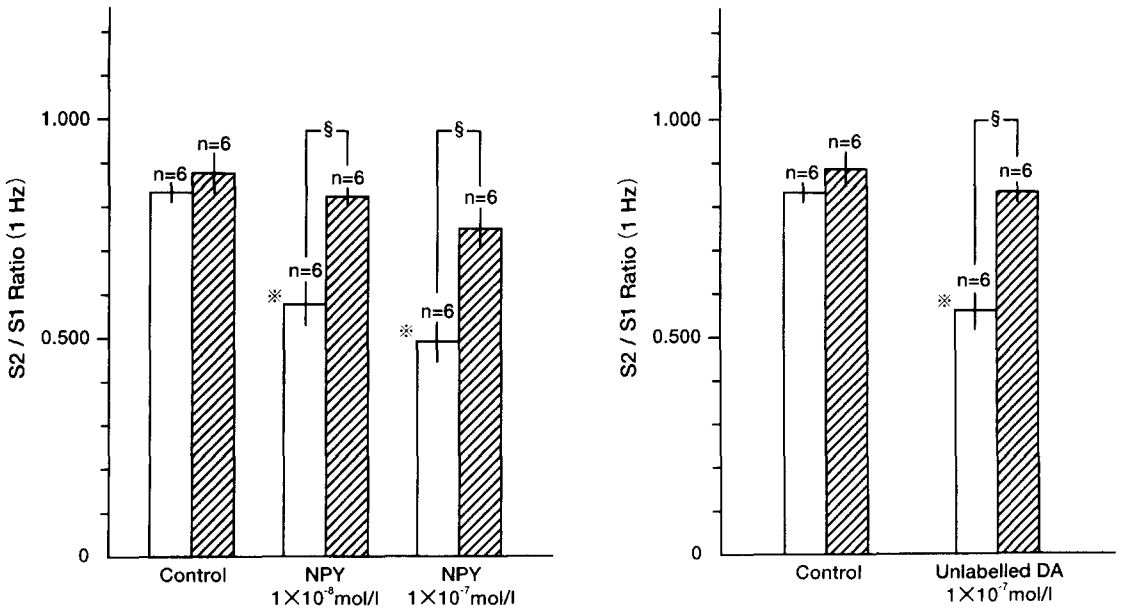

Fig. 1. Effects of neuropeptide Y and unlabelled dopamine on the stimulation-evoked [^{3}H]dopamine release in the pertussis toxin-pretreated striatal slices of Sprague-Dawley rats. The slices of rat striatum were preincubated with pertussis toxin (8 μg/ml) for 1 h at 37°C in an atmosphere of 95% O_2 and 5% CO_2. Subsequently, the slices were incubated in the presence of 0.1 μmol/l of [^{3}H]dopamine for 20 min at 37°C, and the effects of neuropeptide Y and unlabelled dopamine on the stimulation-evoked [^{3}H]dopamine release were determined. Effects of neuropeptide Y and unlabelled dopamine on the stimulation-evoked [^{3}H]dopamine release were expressed as S2/S1 ratios. Values are expressed as means ± S.E.M. NPY, neuropeptide Y; DA, dopamine; open columns, pertussis toxin (−); hatched columns, pertussis toxin (+); asterisk, $P < 0.05$ vs. control value; section sign, $P < 0.05$ between pertussis toxin (−) and pertussis toxin (+).

neuropeptide Y 1×10^{-7} mol/l without pertussis toxin 0.496 ± 0.041, $n = 6$, $P < 0.05$). In pertussis toxin-untreated slices, unlabelled dopamine significantly inhibited the stimulation-evoked [^{3}H]dopamine release on its own. The inhibitory effect of unlabelled dopamine on the stimulation-evoked [^{3}H]dopamine release was also reduced by pertussis toxin (S2/S1 ratio: control with pertussis toxin 0.888 ± 0.041, $n = 6$, control without pertussis toxin 0.837 ± 0.018, $n = 6$, unlabelled dopamine 1×10^{-7} mol/l with pertussis toxin 0.838 ± 0.021, $n = 6$, unlabelled dopamine 1×10^{-7} mol/l without pertussis toxin 0.562 ± 0.038, $n = 6$, $P < 0.05$).

3.3. Effects of neuropeptide Y on [^{3}H]dopamine release in the striatum of SHR and WKY rats

The basal release of [^{3}H]dopamine was not different between SHR and WKY rats (fractional release during b1: SHR $5.870 \pm 0.176\%$ of total tissue radioactivity, $n = 6$, WKY rats $6.056 \pm 0.198\%$ of total tissue radioactivity, $n = 6$). The stimulation-evoked [^{3}H]dopamine release from slices of the striatum was, however, significantly decreased in SHR compared with WKY rats (fractional release during S1: SHR $1.719 \pm 0.034\%$ of total tissue radioactivity, $n = 6$, WKY $2.009 \pm 0.047\%$ of total tissue radioactivity, $n = 6$, $P < 0.05$).

It was demonstrated that neuropeptide Y inhibited the stimulation-evoked [^{3}H]dopamine release to a greater extent in SHR than in WKY rats (S2/S1 ratio: control, SHR 0.815 ± 0.030, $n = 6$, WKY rats 0.806 ± 0.026, $n = 6$, neuropeptide Y 1×10^{-7} mol/l, SHR 0.416 ± 0.016, $n = 6$, WKY rats 0.597 ± 0.027, $n = 6$, $P < 0.05$).

The basal release of [^{3}H]dopamine was not significantly affected by neuropeptide Y in both SHR and WKY rats (b2/b1 ratio: control, SHR 0.844 ± 0.010, $n = 6$, WKY rats 0.823 ± 0.008, $n = 6$, neuropeptide Y 1×10^{-7} mol/l, SHR 0.851 ± 0.025, $n = 6$, WKY rats 0.878 ± 0.024, $n = 6$).

4. Discussion

Previous studies have suggested that neuropeptide Y in the synaptic junctions may functionally influence the dopaminergic nervous systems as a neuromodulator of local circuit neurons in the striatum (Vuillet et al., 1989a,b). We therefore investigated the regulatory mechanisms of neuropeptide Y on dopamine release in rat striatum. The results of the present study demonstrated that neuropeptide Y significantly inhibited the stimulation-evoked [^{3}H]dopamine release in rat striatal slices. This is consistent with our previous reports showing that neuropeptide Y (1×10^{-8}–1×10^{-7} mol/l) reduced the stimulation-evoked [^{3}H]norepinephrine release in the hypothalamus (Tsuda et al., 1989, 1990).

The central dopamine release from nerve terminals is regulated by presynaptic dopamine autoreceptors (D_2 type), because the administration of the dopamine D_2 receptor agonists caused a marked reduction in dopamine release in the striatum (Yokoo et al., 1988). In this study, the blockade of dopamine D_2 receptors by sulpiride significantly attenuated the inhibitory effects of neuropeptide Y on the stimulation-evoked [^{3}H]dopamine release. Although another possibility is that neuropeptide Y acts through some interneurons, the observation strongly suggests that the effect of neuropeptide Y is dependent on dopamine D_2 receptors on dopaminergic nerve terminals. Recent studies have shown that there are specific neuropeptide Y receptors, such as Y_1, Y_2, and Y_3 receptors, in several tissues (Dumont et al., 1993). It would be possible that the specific neuropeptide Y receptors have a role in the regulation of dopamine release in rat striatum, although their functional link to dopamine D_2 receptors is still to be determined.

It is well known that dopamine D_2 receptors in the striatum are coupled to the G_i-proteins (Ohara et al., 1988). Pertussis toxin inactivates the G_i-proteins by adenosine diphosphate-ribosylation of the α-subunit, and this toxin has been widely used to determine the involvement of the G_i-proteins in the receptor-mediated inhibition of adenylate cyclase (Murayama and Ui, 1983). The present study showed that the neuropeptide Y-induced decrease in the stimulation-evoked [^{3}H]dopamine was attenuated in slices pretreated with pertussis toxin. Westlind-Danielsson et al. (1988) demonstrated that neuropeptide Y significantly inhibited adenylate cyclase activity in rat striatum. These findings support the idea that the inhibitory modulation of [^{3}H]dopamine release by neuropeptide Y was, at least in part, mediated by the coupling of the receptors by means of the G_i-proteins. In this study pertussis toxin did not alter the absolute value of the fractional release of [^{3}H]dopamine during S1 and S2 stimulation, although sulpiride increased the electrically stimulated release of dopamine. The difference between the sulpiride effect and the pertussis toxin effect might depend on the sites of action of these agents. Sulpiride directly blocks the function of dopamine D_2 receptors and increases the fractional release of dopamine by reducing the negative feedback regulation of dopamine D_2 receptors. On the other hand, pertussis toxin affects the function of the G_i-proteins, which are partially coupled with dopamine D_2 receptors. It is unlikely that all the G_i-proteins might be coupled with dopamine D_2 receptors. In addition, it remains to be solved whether neuropeptide Y may interact with only dopamine D_2 receptor-mediated G_i-proteins or other coupling proteins, which might partially explain the smaller effect of pertussis toxin on the fractional release of dopamine.

There have been several reports showing that neuropeptide Y modulated the dopamine metabolism in the striatum. Beal et al. (1986) demonstrated that neuropeptide Y stimulated the turnover of dopamine in rat striatum since the content of 3,4-dihydroxy-phenyl acetic acid (DOPAC)

and homovanillic acid (HVA) in the striatum was increased after administration of neuropeptide Y. Heilig et al. (1990) also reported that centrally injected neuropeptide Y increased the content of dopamine and DOPAC in rat striatum. In addition, Kerkerian-Le Goff et al. (1992) showed that intracerebroventricular injection of neuropeptide Y increased the release of dopamine by using a voltammetric method. These findings may be contradictory to our present result showing that neuropeptide Y reduced the release of dopamine from striatal slices. However, Vallejo et al. (1987) proposed that the dopamine turnover was decreased in brainstem and striatum after administration of neuropeptide Y in rats treated with α-methyl-*p*-tyrosine. The reasons responsible for the discrepancy among the results are unknown. In an in vivo study, the sites of action of centrally injected neuropeptide Y may be widespread. It would be possible that neuropeptide Y could influence many neuronal systems, and that the several effects on striatal dopaminergic fibers might be integrated, although the precise role of neuropeptide Y in regulating dopamine metabolism remains to be solved.

Much evidence has shown that abnormalities in the central dopaminergic systems may be involved in the pathogenesis of hypertension (Kolloch et al., 1980; Chiu et al., 1982). On the other hand, it has also been assumed that dopaminergic activity in the central nervous system may cause changes in locomotor activities. It was reported that SHR had greater exploratory behavior, excessive responses behaviorally and physiologically to stimuli, reduced fear reactivity, a lower anxiety level, and increased aquisition to avoidance tasks (Danysz et al., 1983; McCarty, 1983; Van den Buuse et al., 1986). In the present study we showed that the stimulation-evoked [^{3}H]dopamine release was significantly smaller in the striatum of SHR than in the striatum of WKY rats. The finding might be consistent with a previous report demonstrating that the release of [^{3}H]dopamine evoked by electrical stimulation with various frequencies (1–15 Hz) from the striatum was smaller in SHR than in WKY rats (Linthorst et al., 1990). In an in vivo microdialysis study, it was also reported that the release of endogenous dopamine and DOPAC was significantly lower in the striatum of SHR than in the striatum of WKY rats (Linthorst et al., 1991). It would be possible that the alteration in the dopaminergic neurotransmission might be involved not only in blood pressure control, but also in regulating the locomotor and behavioral activities in hypertension. Furthermore, the results of the present study showed that the suppression of dopamine release by neuropeptide Y was more pronounced in the striatum of SHR than in age-matched WKY rats, which might partially explain the decreased release of dopamine in the striatum of SHR. The mechanisms underlying the greater suppression of dopamine release by neuropeptide Y are still uncertain. Radiobinding studies demonstrated the greater density of dopamine D_2 binding sites in the striatum of SHR (Chiu et al., 1982). Although the non-specific neuropeptide Y effect cannot be fully excluded, the increased number of dopamine D_2 binding sites might produce the enhanced sensitivity to neuropeptide Y in SHR. Additional studies should be conducted to assess more thoroughly the possible interactions of neuropeptide Y with central dopaminergic systems and their contribution to the pathophysiology of hypertension.

In summary, the results of the present study showed that neuropeptide Y inhibited the stimulation-evoked [^{3}H]dopamine release partially mediated by presynaptic dopamine D_2 receptors and the pertussis toxin-sensitive G_i-proteins in rat striatum. Furthermore, the greater suppression of dopamine release by neuropeptide Y might be consistent with the idea that the peptide was involved in the regulation of central dopaminergic activity in SHR.

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