ELSEVIER

European Journal of Pharmacology 349 (1998) 163–169

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Characterization of β-phenylethylamine-induced monoamine release in rat nucleus accumbens: a microdialysis study

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Received 24 November 1997; revised 23 February 1998; accepted 3 March 1998

Abstract

In vivo microdialysis was used to investigate the effect of β-phenylethylamine on extracellular levels of monoamines and their metabolites in the nucleus accumbens of conscious rats. At all doses tested (1, 10 and 100 μM), infusion of β-phenylethylamine through the microdialysis probe significantly increased extracellular levels of dopamine in the nucleus accumbens. These increases were dose-related. The increase in dopamine levels induced by 100 μM β-phenylethylamine was not affected by co-perfusion of 4 μM tetrodotoxin. The ability of 100 μM β-phenylethylamine to increase the extracellular level of dopamine was comparable to that of the same dose of methamphetamine. On the other hand, β-phenylethylamine had a much less potent enhancing effect on 5-hydroxytryptamine (5-HT) than dopamine levels. Only the highest dose (100 μM) caused a statistically significant effect on 5-HT levels. Over the dose range tested (1, 10 and 100 μM), β-phenylethylamine had no effect on extracellular metabolite levels of dopamine and 5-HT. The results suggest that β-phenylethylamine increases the efflux of monoamines, preferentially dopamine, without affecting monoamine metabolism, in the nucleus accumbens.

Keywords: β-Phenylethylamine; Dopamine; 5-HT (5-hydroxytryptamine, serotonin); Nucleus accumbens; Methamphetamine; Microdialysis

1. Introduction

β-Phenylethylamine is an endogenous trace amine that has been identified in the mammalian brain such as rodents (Boulton et al., 1990; Paterson et al., 1990), sheep (Reynolds et al., 1980) and humans (Philips et al., 1978). Biochemical studies revealed that the most abundant sites of β-phenylethylamine is in mesolimbic and caudate–putamen structures (Paterson et al., 1990; Philips et al., 1978; Reynolds et al., 1980). β-Phenylethylamine is pharmacologically active in evoking stereotyped behavior, anorexia, and in increasing locomotor activity (Dourish, 1985; Dourish and Boulton, 1981; Dourish et al., 1983; Greenshaw et al., 1983; Jackson, 1975; Kuroki et al., 1990; Moja et al., 1976; Ortmann et al., 1984). β-Phenylethylamine also induces an increase of responding to lateral hypothalamic self-stimulation of rats pretreated with the monoamine oxidase inhibitor L-deprenyl (Greenshaw et al., 1985). In addition to its behavioral effects, β-phenylethylamine has been shown to interact with monoaminergic systems in vitro (Dyck, 1983; Dyck and Boulton, 1989; Hansen et al., 1980; Horn and Snyder, 1972; Locock et al., 1984; Raiteri et al., 1977) and in vivo (Antelman et al., 1977; Bailey et al., 1987; Dyck, 1983; Greenshaw et al., 1985; McQuade and Juorio, 1982; Philips, 1986; Philips and Robson, 1983; Raiteri et al., 1977) animal preparations. Therefore, various behaviors induced by β-phenylethylamine appear to involve release of monoamines. Despite accumulating evidence for the effect of β-phenylethylamine on monoaminergic neurons in the striatum (Antelman et al., 1977; Bailey et al., 1987; Dyck, 1983; Greenshaw et al., 1985; Kuroki et al., 1990; McQuade and Juorio, 1982; Philips, 1986; Philips and Robson, 1983; Raiteri et al., 1977), a structure responsible for stereotypy, little is known how it affects monoaminergic neurotransmission in the nucleus accumbens, a structure responsible for locomotion and self-stimulation behavior.

The present study was undertaken, therefore, to characterize the action of β-phenylethylamine on monoaminergic transmission in the nucleus accumbens. For this purpose, we used a microdialysis technique to assess the effect of

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0014-2999/98/$19.00

intracerebral β-phenylethylamine application on the concentration of dopamine, 5-hydroxytryptamine (5-HT) and their metabolites in the dialysate from the nucleus accumbens of awake rats.

2. Materials and methods

2.1. Subjects and surgery

Male Wistar rats (230–250 g, Japan SLC, Shizuoka, Japan) were used. The animals were individually housed in cages, which were maintained on a 12 h light/dark cycle (lights on at 0700) in a temperature controlled environment (23°C), with food and water available ad libitum. All the procedures for animal treatment and surgery were in accordance with the guideline established by Institute for Experimental Animals of Hamamatsu University School of Medicine and were approved by the local academic committee for animal experiments.

The animals were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and placed in a stereotaxic apparatus with the skull flat between bregma and lambda. The skull was exposed and a hole was drilled, through which a guide cannula was implanted in the nucleus accumbens (1.2 mm anterior, 1.5 mm lateral, and 5.5 mm ventral), according to the atlas of Paxinos and Watson (1986). The cannula was fixed to the skull with dental cement and anchor screws, and then a dummy probe was placed inside the cannula. Animals were allowed to recover for 7 days before experiments were started.

2.2. Microdialysis

At the beginning of the experiment, the dummy probe was replaced with a microdialysis probe (membrane length 3 mm, polyacrylonitrile/sodium methalyl sulfonate copolymer, 0.045 mm in wall width, 0.31 mm in outer diameter, molecular cut-off of 11 000 Da, Hospal, France), which was hand-made according to a similar procedure described elsewhere (Nakahara et al., 1993), and then the nucleus accumbens was perfused with a Ringer solution at a flow rate of 2 μl/min. Following a 3-h stabilization period, dialysates were collected at 20-min intervals in small plastic vials. Three consecutive samples were collected as baseline measurements, and immediately after the third sample the nucleus accumbens was exposed to perfusion with the Ringer solution containing 100 μM β-phenylethylamine (Sigma) to investigate its effect on the dialysate concentrations of monoamines and their metabolites. In addition, the following experiments were carried out using separate groups of animals. First, to investigate the relationship between the β-phenylethylamine concentration and monoamine responses, the nucleus accumbens was perfused with the Ringer solutions containing various concentrations of β-phenylethylamine (1 μM–100 μM), and its effects on the dialysate levels of monoamines were compared. Second, to examine if the release-inducing effects of β-phenylethylamine depend on neuronal firing activity, the nucleus accumbens was co-perfused with the Ringer solution containing 100 μM β-phenylethylamine and 4 μM tetrodotoxin, the sodium channel blocker. Finally, to evaluate the potency of β-phenylethylamine as a releaser of monoamines, monoamine responses in the nucleus accumbens to 100 μM β-phenylethylamine were compared with those to 100 μM methamphetamine, a well known monoamine releaser.

2.3. HPLC analysis

The chromatographic analysis of dialysates was done by reversed-phase high-performance liquid chromatography

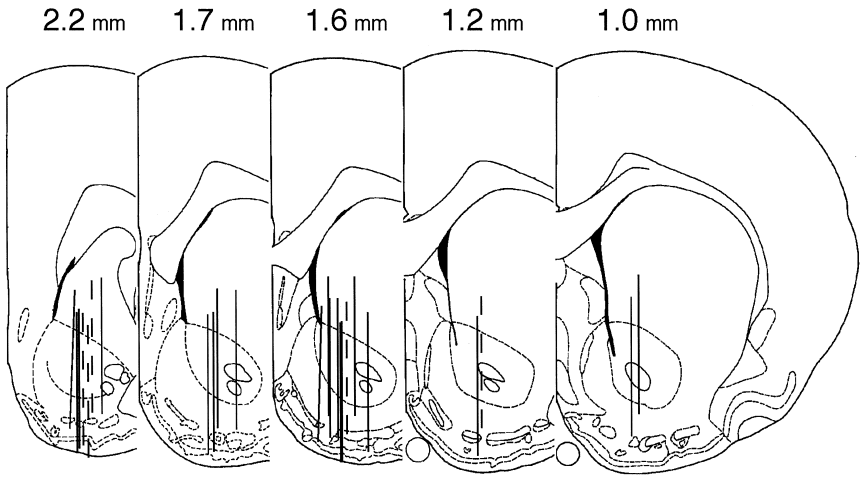

Fig. 1. Illustration of the location of the dialysis probes in the nucleus accumbens. Solid lines indicate probe tracks within the nucleus accumbens that were used once in the experiments, while the dotted line indicates placement that was used in two experiments. The numbers represent the distance rostral to the bregma according to the atlas of Paxinos and Watson (1986).

(HPLC) with electrochemical detection according to the technique described previously (Nakahara et al., 1992). The HPLC system (EICOM, Kyoto, Japan) consisted of an EICOM EP-10 pump, an ECD-100 electrochemical detector with a WE-3G graphite working electrode and a Shimadzu Chromatopack CR-5A integrator. The detector potential was set at +650 mV against a Ag/AgCl reference electrode. Monoamines and metabolites were separated on a reverse-phase Eicompack MA-5ODS column (5 μm, 4.6 mm × 150 mm). The flow rate was 1.2 ml/min, and the sensitivity was set at 2 nA/V full scale. The mobile phase consisted of 70 mM citric acid, 100 mM sodium acetate buffer (pH 4.0) containing 1.01 mM sodium 1-octanesulfonate, 26.9 μM disodium ethylenediaminetetraacetic acid (EDTA), and 17% methanol.

2.4. Histology

At the completion of the experiments, animals were killed with an overdose of sodium pentobarbital, then their brains were removed for the histological verification of the tip location of the probes by visual inspection under the dissecting microscope.

2.5. Statistical analysis

The values of dopamine and 5-HT in the dialysate are expressed as raw data, since basal 5-HT levels in the nucleus accumbens were undetectable in some animals. The detection limit in our assay was 0.31 fmol. Therefore, undetected 5-HT levels were assigned to a value of 0.31 fmol when statistics was performed. The values of dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) are expressed as percent change from basal levels. The basal level represents the mean of the values obtained from the first three samples. The time course data were analyzed using a two-way, repeated measures analysis of variance (ANOVA) followed by a least significant difference test for comparisons between responses to β-phenylethylamine, methamphetamine and control values. Other neurochemical data were analyzed using a one-way ANOVA followed by a Dunnett's test or a least significant difference test for comparisons of responses to β-phenylethylamine or methamphetamine with basal (or control) values. The level of significance was set at $P < 0.05$.

3. Results

Fig. 1 depicts the location of the dialysis probes in the nucleus accumbens. The probes were placed in the core or in the medial shell regions of the nucleus accumbens.

The basal concentration of neurochemicals in control animals (means ± S.E.M., $n = 6$) was 10.9 ± 5.0 fmol/sample for dopamine, 15.6 ± 1.8 pmol/sample for DOPAC, 9.1 ± 1.7 pmol/sample for HVA, 0.9 ± .0.3 fmol/sample for 5-HT and 4.6 ± .4 pmol/sample for 5-HIAA. As shown in Fig. 2, perfusion of 100 μM

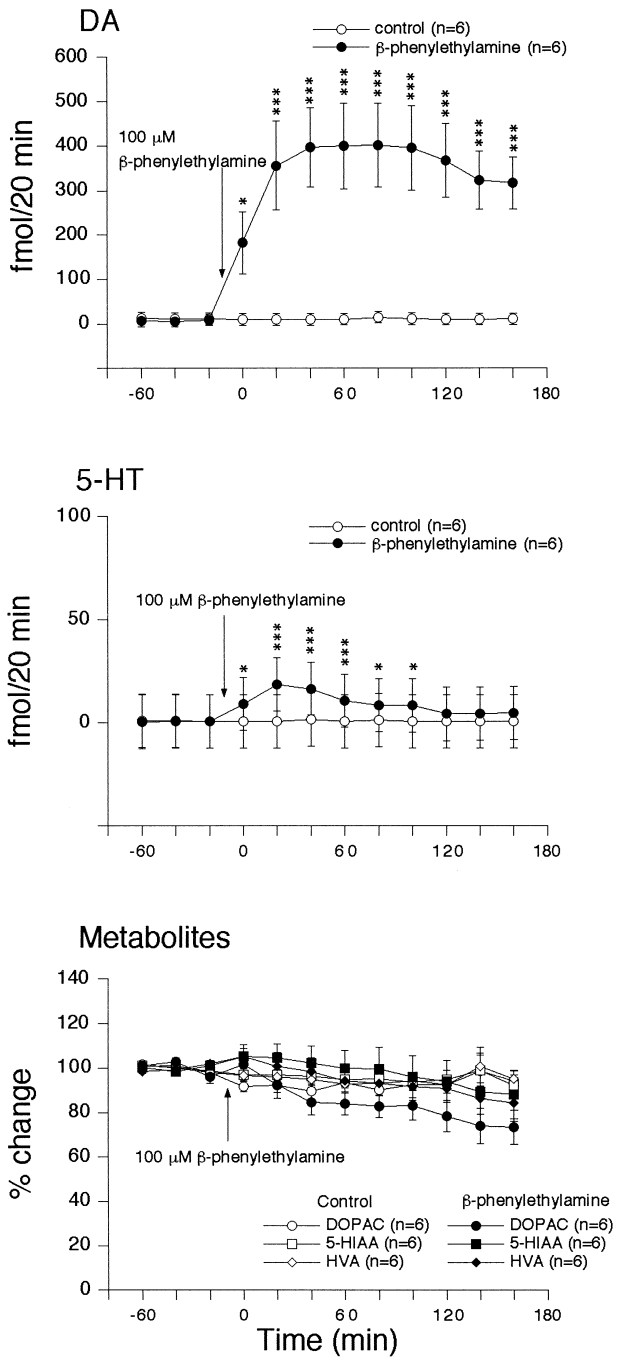

Fig. 2. Effect of perfusion of 100 μM β-phenylethylamine on the dialysate levels of dopamine, 5-HT and their metabolites in the nucleus accumbens. Symbols and bars represent means ± S.E.M. The time course data were analyzed with a two-way, repeated measures ANOVA followed by a least significant difference test for multiple comparisons. F scores for drug were: $F(1,10) = 22.82$, $P < 0.001$ for dopamine; $F(1,10) = 11.46$, $P < 0.001$ for 5-HT. *Significant at $P < 0.05$ and ***significant at $P < 0.001$ compared with the respective control values. Abbreviation: DA, dopamine.

β-phenylethylamine in the nucleus accumbens caused a huge increase in the dialysate level of dopamine, as compared to controls, with the maximal effect of 401.8 ± 102.9 fmol/sample being reached after 80 min. Perfusion with 100 μM β-phenylethylamine also induced a significant increase in the dialysate level of 5-HT (maximum: 18.7 ± 6.6 fmol/sample). However, this increase was much smaller than that seen in dopamine levels. Metabolite levels of dopamine and 5-HT in the dialysate were not affected by the β-phenylethylamine injection. Fig. 3 demonstrates that accumbal β-phenylethylamine perfusion increased the efflux of dopamine in a concentration-related manner. The increase in dialysate concentrations of dopamine from basal levels was 254.6 ± 18.4%, 1473.9 ± 154.8%, and 6269.9 ± 1032.3%, respectively, at doses of 1, 10, and 100 μM of β-phenylethylamine. On the other hand, β-phenylethylamine increased the efflux of 5-HT (284.3 ± 49.2% of basal values) only at a highest dose of 100 μM. The effect of pretreatment with 4 μM tetrodotoxin and subsequent treatment with 100 μM β-phenylethylamine on the dialysate level of dopamine and 5-HT is shown in Fig. 4. Even when nerve-firing activity

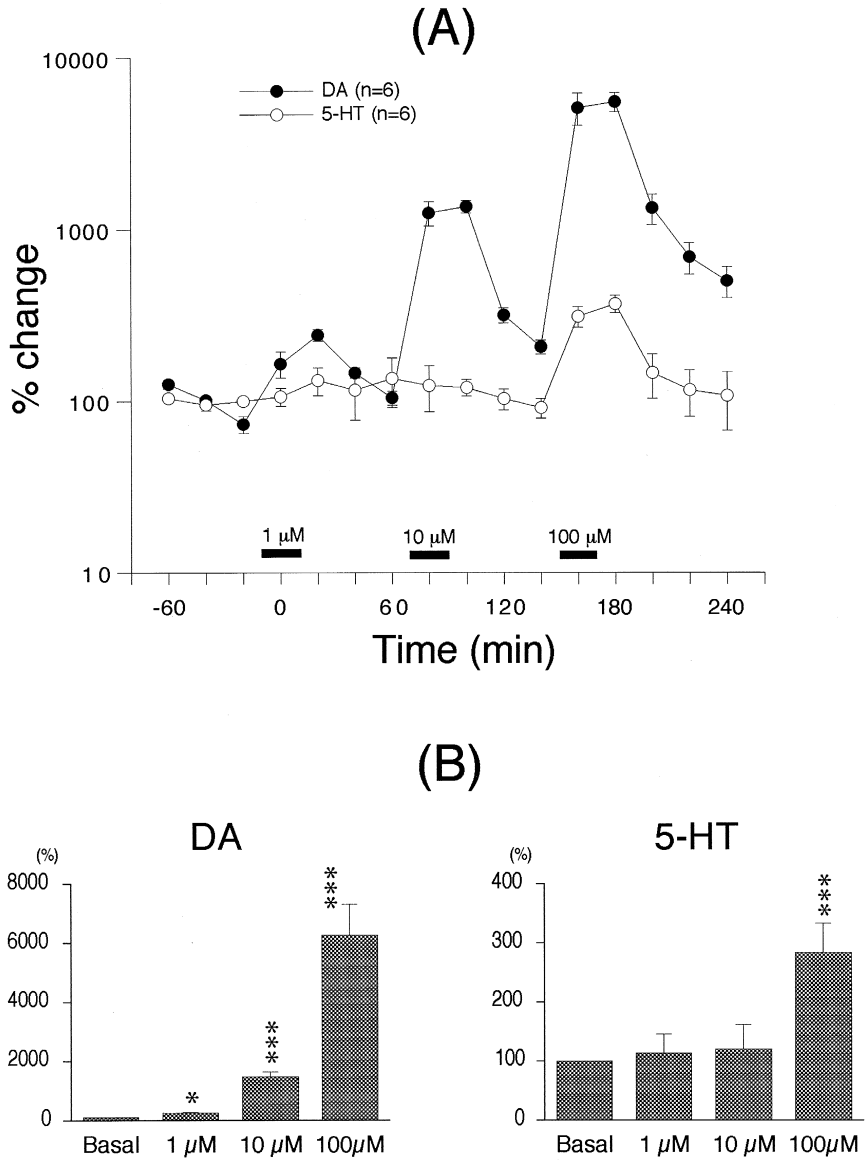

Fig. 3. (A) Effect of various concentrations of β-phenylethylamine (1, 10, 100 μM) in the perfusion medium on the dialysate levels of dopamine and 5-HT. Symbols and bars represent means ± S.E.M. Each dose of β-phenylethylamine was perfused for a period of 20 min after a washout period of 60 min. (B) Dose–response data were transformed into data points that represented the peak of four 20 min dialysis samples after each dose. The transformed data were analyzed with a one-way ANOVA followed by Dunnett's multiple comparisons. F scores for dose were: $F(3,20) = 30.78$, $P < 0.001$ for dopamine; $F(3,20) = 5.83$, $P < 0.001$ for 5-HT. ∗Significant at $P < 0.05$ and ∗∗∗significant at $P < 0.001$ compared with the respective basal values. Abbreviation: DA, dopamine.

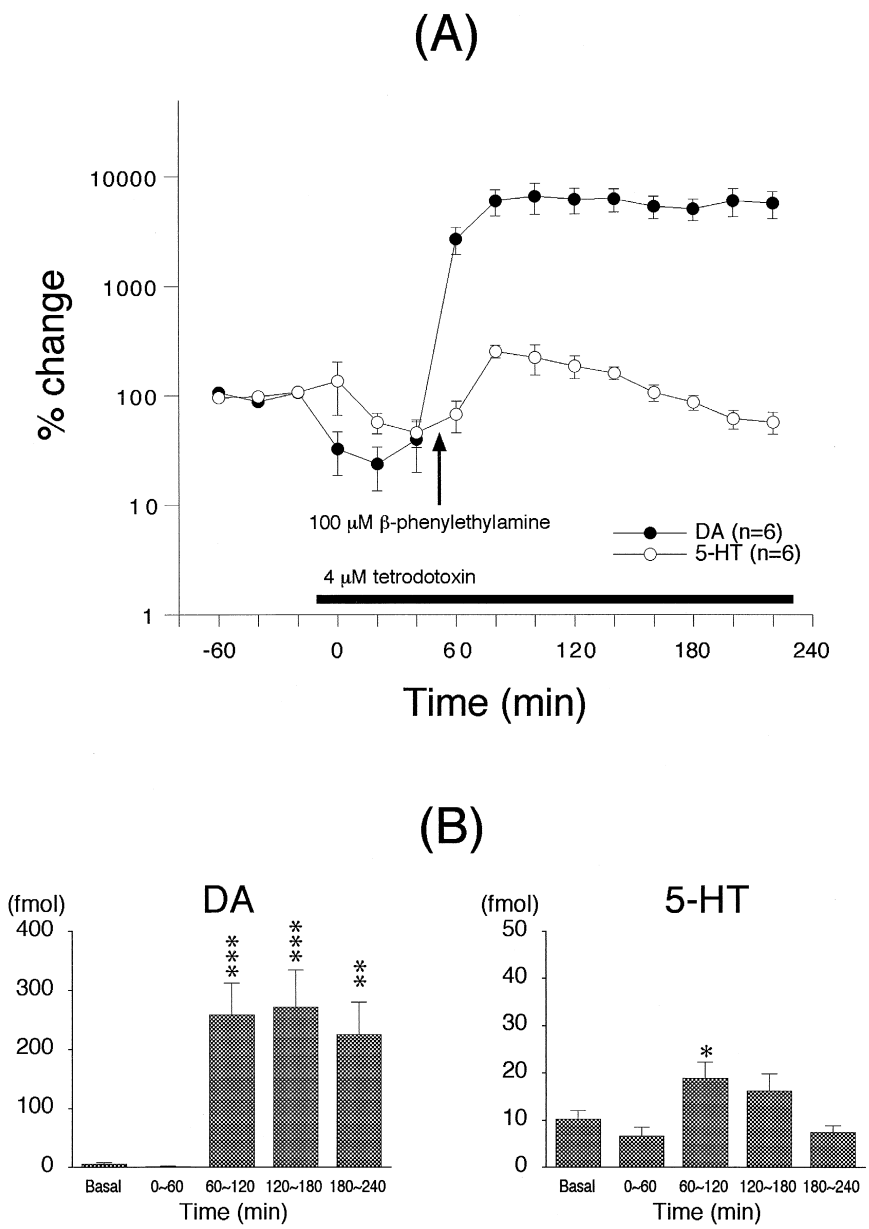

Fig. 4. (A) Effect of perfusion of 4 μM tetrodotoxin and co-perfusion of 100 μM β-phenylethylamine on the dialysate levels of dopamine and 5-HT in the nucleus accumbens. Symbols and bars represent means $\pm$ S.E.M. (B) Time course data were transformed into data points that represented the average of three 20 min dialysis samples per hour. The transformed data were analyzed with a one-way ANOVA followed by a least significant difference test for multiple comparisons. F scores for dose were: $F(4,25) = 9.32$, $P < 0.001$ for dopamine; $F(4,25) = 4.21$, $P < 0.05$ for 5-HT. Following perfusion of tetrodotoxin, dialysate levels of dopamine and 5-HT were decreased to $36.0 \pm 11.7\%$ and $75.5 \pm 25.6\%$ of basal values, respectively. On the contrary, after co-perfusion of β-phenylethylamine, dopamine and 5-HT levels were significantly increased to $5911.1 \pm 1451.1\%$ and $186.3 \pm 32.7\%$ of basal values, respectively. $*$Significant at $P < 0.05$, $**$significant at $P < 0.01$ and $***$significant at $P < 0.001$ compared with the basal values. Abbreviation: DA, dopamine.

was inhibited by tetrodotoxin, β-phenylethylamine significantly increased the efflux of dopamine and 5-HT to a similar level compared with β-phenylethylamine alone. Finally, the potency of β-phenylethylamine as a monoamine releaser was compared with methamphetamine. Both perfusions of β-phenylethylamine and methamphetamine at a concentration of 100 μM increased the dopamine efflux to a similar extent (355.3 ± 79.0 fmol/sample for β-phenylethylamine and 385.3 ± 160.0 fmol/sample for methamphetamine). However, 100 μM methamphetamine induced a 7.9-fold increase in the efflux of 5-HT as compared with the same dose of β-phenylethylamine (12.1 ± 3.5 fmol/sample for β-phenylethylamine, 95.5 ± 25.1 fmol/sample for methamphetamine). Methamphetamine significantly reduced DOPAC levels (a maximal decrease: $49.9 \pm 8.5\%$ of control values, $F(2, 14) = 10.67$, $P < 0.01$), whereas it did not affect HVA or 5-HIAA levels.

4. Discussion

The present study clearly demonstrates that β-phenylethylamine, when locally administered into the nucleus accumbens through a microdialysis probe, caused an increase in the dialysate levels of monoamines, preferentially dopamine, but no change in their metabolite levels.

Infusion of 100 μM β-phenylethylamine into the perfusion medium induced a large increase in the dialysate level of dopamine, as compared to controls, while it caused a small increase in the dialysate level of 5-HT (Fig. 2). A recent microdialysis study has showed that systemic administration of β-phenylethylamine elicits a remarkable increase in dialysate concentrations of dopamine in the striatum (Kuroki et al., 1990), which is similar to the β-phenylethylamine-induced increase in the efflux of dopamine observed in the nucleus accumbens. It is suggested, therefore, that β-phenylethylamine may induce a common effect in any of the dopaminergic neurons in the brain.

The maximal increase in the dopamine concentration following perfusion with 100 μM β-phenylethylamine was about 6300% of control values (Fig. 3B), which was comparable to that induced by the same dose of methamphetamine. Thus, this compound may possess the same ability as methamphetamine to increase the efflux of dopamine. On the other hand, the maximal β-phenylethylamine-induced increase in the 5-HT concentration was about 280% of control levels (Fig. 3B). This increase was smaller than that observed on dopamine efflux. Moreover, the 5-HT response to this dose was much smaller (approximately 0.13 times) than that of methamphetamine. Thus, despite its structural similarity with methamphetamine, β-phenylethylamine may have a much lower capability than methamphetamine for enhancing the 5-HT efflux. Previous in vivo and in vitro studies have reported that β-phenylethylamine inhibits the uptake of dopamine and 5-HT (Bailey et al., 1987; Dyck, 1983; Raiteri et al., 1977). Therefore, it remains to be possible that inhibition of the uptake mechanisms by β-phenylethylamine, like methamphetamine, may partially contribute to the increased dialysate levels of dopamine and 5-HT. Further investigation is necessary to resolve this issue. On the other hand, unlike methamphetamine, even the highest dose (100 μM) of β-phenylethylamine did not cause any effect on dialysate levels of dopamine metabolites, DOPAC and HVA, as well as a 5-HT metabolite, 5-HIAA (Fig. 2). It has been also reported that a higher concentration (500 μM) of β-phenylethylamine increases the dialysate level of 3-methoxytyramine (3-MT), a dopamine metabolite (Bailey et al., 1987). Therefore, it seems unlikely that the observed increase in dopamine and 5-HT levels may be due to inhibition of monoamine metabolism by β-phenylethylamine.

The increase in dopamine and 5-HT levels caused by 100 μM β-phenylethylamine seems to be independent of neuronal activity, since pretreatment with tetrodotoxin, the blocker of voltage-dependent sodium channels, could not completely suppress the β-phenylethylamine-induced response of dopamine and 5-HT (Fig. 4). Probably, this dose of β-phenylethylamine may act as a displacer of monoamines from the storage sites as well as an enhancer of exocytosis of vesicular contents in the brain (Knoll et al., 1996; Paterson et al., 1990). Furthermore, since the increase in the dialysate levels of 5-HT was observed only at the highest dose of β-phenylethylamine, it seems likely that β-phenylethylamine may be taken up into dopaminergic terminals more selectively than into serotonergic terminals and consequently may stimulate the release from cytoplasmic pools of dopamine much more greatly than of 5-HT. Taken together, our data suggest that, at the high dose, β-phenylethylamine may facilitate a vesicular and/or cytoplasmic release of monoamines, or may inhibit their uptake, and its action may be much stronger on dopamine than 5-HT terminals in the nucleus accumbens.

In summary, β-phenylethylamine was capable of increasing the efflux of monoamines, dopamine selectively, without altering their metabolite levels in the nucleus accumbens. The β-phenylethylamine-induced monoamine increase was almost nerve-impulse-independent. Although the precise mechanism of action of β-phenylethylamine on monoamine neurons requires further studies, the compound may act preferentially on dopaminergic transmission in the nucleus accumbens.

Acknowledgements

This work was supported in part by a scientific research grant from the Ministry of Education, Science and Culture of Japan, No. 06610066. We thank Norio Suzuki for performing the histological analysis.

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