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ORIGINAL PAPER

Tactile skin stimulation increases dopamine release in the nucleus accumbens in rats

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Abstract We investigated the effect of mild (non-noxious) tactile stimulation (stroking) of skin on dopamine (DA) release in the nucleus accumbens (NAc) of rats. A coaxial microdialysis probe was stereotaxically implanted in the NAc and perfused with modified Ringer's solution. Dialysate output from consecutive 5-min periods was injected into a high-performance liquid chromatograph and DA was measured using an electrochemical detector. Bilateral tactile stimulation of the back for 5 min significantly increased DA release in conscious and anesthetized animals. Increased DA release was observed by stimulation of the contralateral, but not ipsilateral, back. DA secretion was also increased with stimulation of the forelimb, hindlimb, and abdomen. These effects were abolished after lesioning the ventral tegmental area (VTA). In contrast, noxious stimulation (pinching) of these areas had no effect on DA secretion. In conclusion, innocuous mechanical stimulation of the skin increases DA release in the contralateral NAc via the VTA.

Keywords Tactile skin stimulation · Massage · Dopamine · Nucleus accumbens · Ventral tegmental area · Microdialysis

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Introduction

Tactile stimulation of the skin affects various bodily functions, including the promotion of growth in premature babies [1–4], improvement of respiration [5] and the immune response [6], reduction of blood pressure and heart rate [7–9], decrease of adrenal catecholamine secretion [10, 11], increase of spinal cord blood flow [12, 13], and pain control during labor [14, 15].

Tactile stimulation also produces psychological effects such as relaxation [15], the alleviation of anxiety and depression during labor [14], and the reduction of lassitude, anxiety, and mood disorders in patients with cancer [16]. That the psychological effects evoked by touch therapy involve stimulation of dopamine (DA) or serotonin secretion is suggested by their increased levels in the urine following tactile skin stimulation [17]; however, there is no direct evidence of their increased release in the brain. In order to establish the psychological effects of touch therapy, direct evidence is needed to show that tactile stimulation actually changes the release of these neurotransmitters from the brain areas involved in psychological functions.

The dopaminergic projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) is thought to play a key role in motivational and reward processes [18, 19].

In addition, DA in the NAc plays an important role in the pathophysiology of anxiety and depression [20–24]. In the present study, we hypothesized that tactile stimulation would increase DA release in the NAc. We first performed experiments in rats under anesthesia in order to determine if stroking has a direct effect on DA release in the absence of emotion or conscious perception. Then, the effects of stroking under anesthesia were compared with its effects during consciousness. Lastly, the effects of noxious mechanical stimulation of the skin on DA release were investigated.

Materials and methods

All experiments were conducted in accordance with the Japanese Physiological Society Guide for the Care and Use of Laboratory Animals, and the study was approved by the animal ethics committee of the International University of Health and Welfare.

Animals

The experiments were performed on 36 male Wistar rats (270–350 g). The animals were kept in a temperature-controlled room (23 ± 1 °C) that was lit between 0800 and 2000 hours (Showa, Tokyo). Commercial rodent chow (Labo-MR stock; Nosan, Kanagawa) and tap water were provided ad libitum. Unless otherwise stated, the animals were stroked for 5–10 min every day for at least 2 weeks before the experiment for habituation (we refer to these animals as habituated rats). In addition, some animals were kept without any tactile stimulation except during the acute experiments (we refer to these animals as naïve rats).

Implantation of the guide cannula

Three days prior to the experiment, the rats were anesthetized with pentobarbital (60 mg/kg, i.v.) and stereotaxically implanted with a Gauge guide cannula (diameter 0.5 mm, AG-8; Eicom, Kyoto, Japan) containing a removable obturator (diameter 0.35 mm, AD-8; Eicom), aimed at the left NAc. The placement coordinates (obtained from Paxinos and Watson [25]) were AP +1.6 mm, DV −5.8 mm, ML +1.4 mm. The guide cannula was secured to the skull with a screw and dental cement. Immediately after surgery, the animals were transferred to individual testing cages and allowed to acclimatize for 3 days prior to the experiment.

General experimental procedures

The experiments were performed under either anesthesia or consciousness. Anesthesia was induced with urethane (1.1 g kg^{-1} i.p.). The trachea was intubated for spontaneous breathing. The core temperature was maintained at 37.0 ± 0.1 °C with a heating pad and an infrared lamp (ATB-1100; Nihon-Kohden, Tokyo). Throughout the experiment, the depth of anesthesia was routinely judged by observing the corneal and flexion reflexes.

Implantation of the microdialysis probe and sampling of the dialysate

On the morning of the day of the experiment, a concentric microdialysis probe with a 2-mm membrane (220 μm o.d., 50,000 MW cut-off, A-I-8-02; Eicom) was inserted into the left NAc via the previously implanted guide cannula (Fig. 1). The inlet of the probe was connected to a Teflon tube (JT-10; Eicom) via a Biton tube (JB-30; Eicom), and perfused with modified Ringer's solution (Na^+ 147 mM, K^+ 4 mM, Ca^{2+} 1.15 mM) at a speed of 2 μl/min. The outlet of the probe was also connected to a Teflon tube via a Biton tube, and the Teflon tube was directly connected to the autoinjector of the high-performance liquid chromatograph (HPLC), so that pooled perfusate samples could be injected every 5 min for analysis. In the experiments on conscious animals, the inlet and outlet tubes were connected to a swivel located in a counter-balanced beam to minimize discomfort.

The in vitro recovery rate of DA recorded by individual microdialysis probes varied between 8.9 and 10.8%. Therefore, in order to avoid the differences in the recovery rate of each probe, the DA concentration in the dialysate was calculated at 10.0% of recovery.

Measurement of DA

DA was measured using a HPLC with an electrochemical detector (HPLC-ECD; Eicom). The mobile phase, which

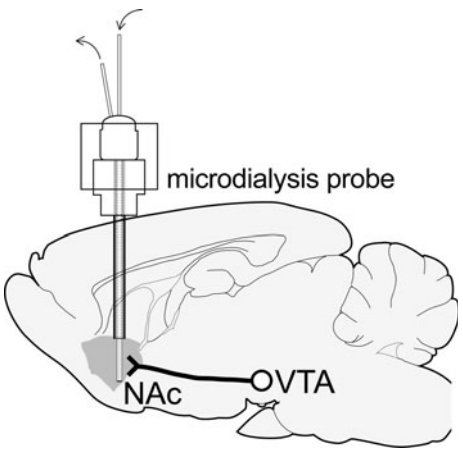

Fig. 1 The location of the microdialysis probe in the NAc and the projection of dopaminergic neurons from the VTA. *NAc* nucleus accumbens, *VTA* ventral tegmental area

consisted of 0.1 M sodium phosphate buffer (pH 6.0), 500 mg/l sodium 1-decanesulfonate, 500 mg/l EDTA 2Na, and 1% methanol, was pumped at a rate of 0.5 ml/min. Separation of DA was accomplished on a reverse-phase column (4.6 Φ × 30 mm; EICOMPAK PP-ODS), and its amount was measured using a graphite electrode (WE-3G; Eicom) set at a detector potential of +400 mV against an Ag/AgCl reference electrode. The coefficient of variation of this method for a standard solution of 1 fmol μl^{-1} was 0.87% ($n = 8$).

Cutaneous stimulation

Innocuous mechanical stimulation of the skin was delivered as manual stroking with a pressure of ca. 80–100 mmH_2O, which was the pressure employed in our previous studies [8, 9], to the forelimb (the area between the shoulder and wrist joints), back (the area between the inferior angle of the scapula and iliac crest), abdomen (the area between the xiphoid process and iliac crest), or hindlimb (the area between the groin and knee joint) of habituated rats. For stimulation of the abdomen, a lighter pressure of ca. 15 mmH_2O was also employed. The experimenter regulated the magnitude of the stimulus pressure by comparing it with the pressure (80–100 mmH_2O) applied to a balloon connected to a manometer. The stimulation was delivered for 5 min at a speed of approximately 4–5 cm/s with a frequency of 65–75 strokes per min (1.08–1.25 Hz). In the experiments with the conscious animals, the neck of the animal was lightly restrained by the experimenter's left hand and gently stroked on the back by the right hand. Noxious mechanical stimulation was given by pinching, which consisted of applying a surgical clamp (3–5 kg force) bilaterally for 5 min to the same skin areas, namely the forelimb, back, abdomen, or hindlimb (approximately 1 cm^2). Both sets of stimuli were applied 1–3 times per rat, and data from identical procedures were pooled to produce an averaged response for each animal.

Lesioning the ventral tegmental area

A coaxial electrode (outer diameter 100 μm) was stereotaxically implanted into the left VTA (AP 3.1 mm, ML 0.8 mm from lambda, DV 8.1 mm from cortical surface), and the VTA was electrically lesioned via the electrode (500 μA anodal DC current, for 1 min) at 2–3 h before the experiment.

Probe placement verification

After completion of the experiment, the rat was killed by an overdose of pentobarbital sodium (50 mg). The probe was removed and the brain was taken out of the skull and fixed in formalin for more than 2 weeks. Coronal (40 μm) sections were stained with hematoxylin and eosin, and examined microscopically for the precise location of the microdialysis probe by referring to the atlas of Paxinos and Watson [25]. The placement of the microdialysis probe was confirmed to be in the NAc for all of the rats used in this study.

Statistical analysis

Data were expressed as the mean ± SD. Comparisons of group differences were made using Student's t test or analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. Probability values of <5% were considered significant.

Results

Responses of DA release to stroking of the bilateral back in anesthetized animals

The basal DA output in the NAc dialysate in the sham experiments (anesthetized but unstimulated condition; $n = 6$) was 10.3 ± 5.8 fmol 10 μl^{-1} (i.e., 10.3 ± 5.8 fmol 10 min^{-1}), and sequential samplings of the dialysate were stable (sham experiments) over a 40-min collecting period (Fig. 2a). When the stroking stimulus was applied to the back bilaterally in the same anesthetized animals ($n = 6$), the concentration of DA (basal concentration: 9.3 ± 6.4 fmol 10 μl^{-1}) in the NAc dialysate increased (Fig. 2b). This increase was statistically significant during the sampling periods of 0–10 min after the onset of the 5-min stimulation. The DA concentration reached 114 ± 6% of the pre-stimulus control value during the stimulation period, and 110 ± 10% during the period of 5–10 min after the onset of stimulation. In the VTA-lesioned animals ($n = 6$), the basal DA concentration in the NAc dialysate decreased to 4.1 ± 2.2 fmol 10 μl^{-1}, and bilateral stroking of the back elicited no statistically significant changes (Fig. 2c).

Responses of DA release to stroking of various cutaneous areas

The effects of stroking the various skin areas on DA output were compared in the same 6 animals as shown in Fig. 2a, b. An increase up to 109 ± 5% of the pre-stimulus control value was found with bilateral forelimb stimulation, and up to 108 ± 4% with bilateral hindlimb stimulation (Fig. 3). In contrast, stroking stimulation applied to the abdomen with 80 mmH_2O pressure (the same pressure applied to the

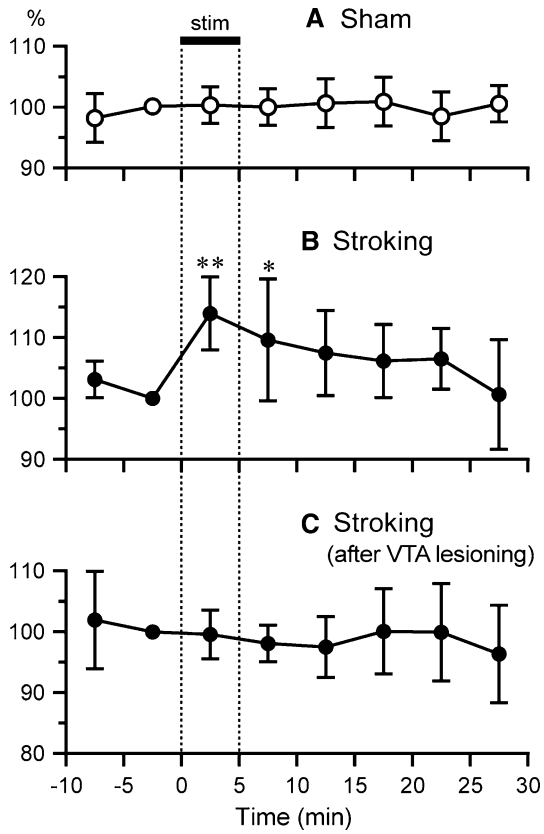

Fig. 2 DA release in the NAc in response to bilateral stroking of the back in the anesthetized animals. *Ordinates* response magnitude is expressed as a percentage of the pre-stimulus control value. *Abscissa* 0 the onset of stimulation. The data are mean ± SD. *Horizontal bar* the 5-min stimulus period. **a** Sham experiments, **b** bilateral stroking of the back, **c** bilateral stroking of the back after VTA lesioning. $*p < 0.05$, $**p < 0.01$, compared with the pre-stimulus control value. $n = 6$

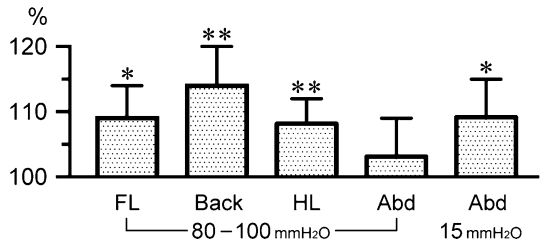

Fig. 3 DA release in the NAc in response to stroking of the various segmental skin areas in the anesthetized animals. Peak responses are compared. *Ordinates* response magnitude is expressed as a percentage of the pre-stimulus control value. *FL* forelimb, *HL* hindlimb, *Abd* abdomen. Stroking at a pressure of 80–100 mmH_2O was applied to the FL, back, HL, and Abd. In addition, the abdomen was also stroked at a pressure of 15 mmH_2O. $*p < 0.05$, $**p < 0.01$, compared with the pre-stimulus control value. $n = 6$

other skin areas) did not produce any statistically significant increases in the DA concentration. However, when the stimulus pressure applied to the abdomen was reduced to

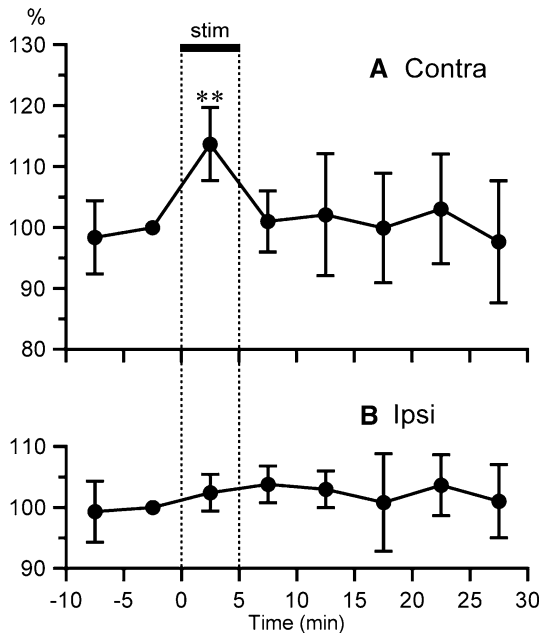

Fig. 4 DA release in the NAc in response to contralateral (**a**) or ipsilateral stroking (**b**) of the back in the anesthetized animals. $n = 6$. See Fig. 2 for other details

15 mmH_2O, the DA concentration increased (109 ± 6% of the pre-stimulus control value).

Effect of laterality of the stroking stimulation on DA release

The effects of stimulus laterality on DA release were examined in another cohort of anesthetized animals ($n = 6$). When stroking stimulation of the back was applied contralaterally to the site of DA measurement, the concentration of DA in the NAc dialysate increased (114 ± 6% of the pre-stimulus control value) during the stimulation period (Fig. 4a). The DA concentration returned to the pre-stimulation control level immediately after the cessation of stimulation (5–10 min after the onset of stimulation). In contrast, when stroking stimulation of the back was applied ipsilaterally to the site of DA measurement, the concentration of DA in the NAc dialysate did not change over the 30-min period after the onset of stimulation (Fig. 4b).

Responses of DA release to pinching of various cutaneous areas

The effects of noxious mechanical stimulation, i.e., pinching, of the skin on DA release were investigated in another cohort of anesthetized animals ($n = 6$). The DA output in the NAc was unchanged with bilateral pinching of the back (Fig. 5a). Similarly, no statistically significant changes in DA release were observed with bilateral

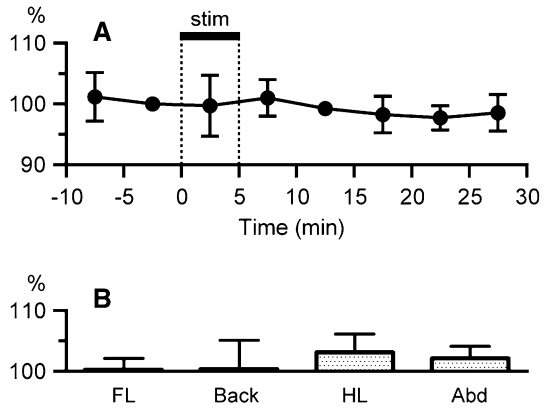

Fig. 5 DA release in the NAc in response to pinching of the various segmental skin areas in the anesthetized animals. **a** Pinching was applied bilaterally to the back for 5 min. **b** Responses during the stimulus period are compared. *Ordinates* response magnitude is expressed as a percentage of the pre-stimulus control value. $n = 6$. See Figs. 2 and 3 for other details

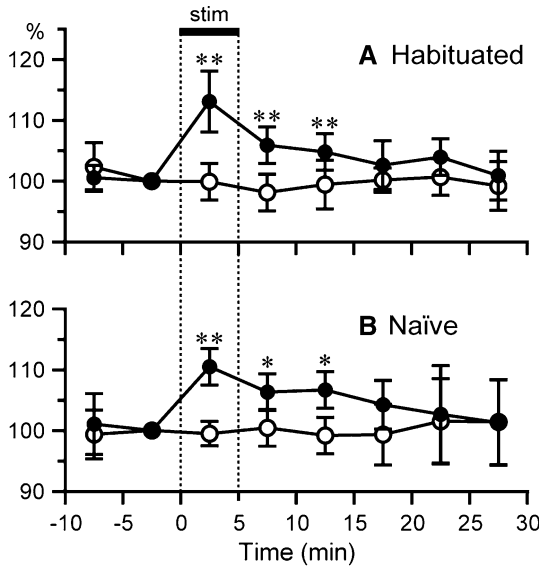

Fig. 6 DA release in the NAc in response to bilateral stroking of the back in the conscious animals. *Closed circles* stroking experiment, *open circles* sham experiment. **a** Responses in habituated animals in which stroking stimulation was applied for 5–10 min every day for more than 2 weeks before the experiments began. **b** Responses in the naïve animals that did not receive stroking stimulation. $n = 6$. See Fig. 2 for other details

pinching of other areas including the forelimb, back, hindlimb, and abdomen (Fig. 5b).

Responses of DA release to stroking of the bilateral back in conscious animals

DA release in the NAc to stroking of the bilateral back was investigated in conscious animals. One group of conscious animals was stroked every day for 5–10 min for more than 2 weeks before the experiments began (habituated rats; $n = 6$). In the absence of stimulation, the basal DA output of the dialysate was 12.3 ± 7.0 fmol 10 μl^{-1} and was stable over the 40-min collection period (Fig. 6a). When stroking stimulation was applied to the back bilaterally in the habituated rats, the concentration of DA in the NAc dialysate increased (Fig. 6a). This increase was statistically significant during 3 consecutive sampling periods (0–15 min) after the onset of 5-min stimulation, with a peak of $113 \pm 5\%$ of the pre-stimulus control value during the stimulation period, $106 \pm 3\%$ during the period of 5–10 min, and $105 \pm 3\%$ during the period of 10–15 min after the onset of stimulation. There was a modest increase in DA secretion at 15–20 min after the onset of stimulation; however, this was not statistically significant.

In naïve (i.e., not previously exposed to stroking) conscious rats ($n = 6$), the basal output of DA in the NAc was 11.7 ± 8.8 fmol 10 μl^{-1} and was stable over a period of 40 min (Fig. 6b). The basal values were similar to those found in habituated rats and there was no statistically significant difference between the habituated and naïve rats. The concentration of DA in the dialysate increased in response to the bilateral stroking as it did in the habituated rats (Fig. 6b). This increase was statistically significant during the first 15 min after the onset of stimulation, reaching $110 \pm 3\%$ of the pre-stimulus control value during the 5-min stimulation period, and $106 \pm 3\%$ at 5–10 min and $107 \pm 3\%$ at 10–15 min after the onset of stimulation.

Discussion

The present study demonstrated, for the first time, that innocuous tactile stimulation, but not noxious pinching stimulation, of the skin increases DA release in the NAc of conscious and anesthetized animals. Our results show that innocuous mechanical stimulation can directly stimulate DA release in the NAc in the absence of conscious perception or emotion. Furthermore, the increases of DA release were generally observed in response to tactile stimulation of various segmental skin areas, but it was only produced by stimulation of the contralateral side to where DA release was measured.

Clinical studies show that tactile stimulation (massage) reduces depressed mood and anxiety, for example, in depressed pregnant women, women diagnosed with breast cancer, subjects with lower back pain, and adolescent patients with bulimia [17, 26–29]. In these studies, the concentration of DA and serotonin in the urine increased after massage, suggesting that the effects of massage on depression and anxiety may be partly due to an increase in the release of DA and/or serotonin in the brain; however,

there is, as yet, no direct evidence of this possibility. The present study provides the first experimental evidence that tactile stimulation increases DA release in the NAc (serotonin was not investigated in the present study). There is strong evidence that this nucleus is involved in the emergence of depression and anxiety [20–24]. These results suggest that tactile or massage therapy can dampen depression and anxiety via the activation of dopaminergic neurons in the NAc.

Only tactile stimulation applied to the side contralateral, not to the side ipsilateral, to the NAc where DA was measured was effective in increasing DA release. Since this effect was abolished after lesioning the VTA, we suggest that cutaneous tactile stimulation excites the dopaminergic neurons located in the VTA contralateral to the site of stimulation (Fig. 7). In accordance with the present results, unilateral injection of 6-hydroxydopamine in the VTA of rats results in inattention to sensory stimuli originating in the contralateral body surface [30]. Sensory input mainly enters the contralateral side of the brain, and tactile input enters the brain via two ascending limbs of the spinal cord, one ascends in the ipsilateral and the other ascends in the contralateral spinal cord to the side of the stimulation. We did not clarify which of these ascending limbs contributes to DA release in the NAc.

Although it is strongly suggested that tactile inputs stimulate dopaminergic neurons in the VTA, there is no evidence of a direct connection between the VTA and sensory relay nuclei, such as those in the thalamus. However, it is known that DA release in the NAc is stimulated presynaptically by glutamate, which is released from axonal projections originating in the paraventricular nucleus of the thalamus (PVT) [31]. Therefore, there is the possibility

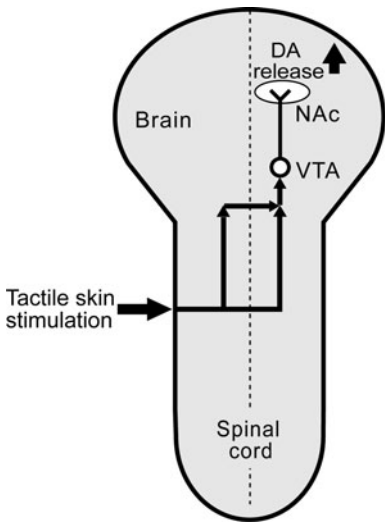

Fig. 7 Summary of the present results. Tactile stimulation of the skin increases DA release in the contralateral NAc. *DA* dopamine, *NAc* nucleus accumbens, *VTA* ventral tegmental area

that sensory input stimulates the glutaminergic neurons in the PVT, which in turn increase DA release by stimulating the terminals of dopaminergic neurons originating from the VTA. Further investigation is needed to clarify how sensory stimulation might increase DA synaptic release in the NAc.

The increase in DA release in the NAc was found with tactile stimulation (80–100 mmH_2O) applied to various skin areas including the back, forelimb, and hindlimb, but not the abdomen. However, stimulation of the abdominal area was effective when applied with lighter pressure (15 mmH_2O). It may be that the lighter stimulus avoids stimulation of the abdominal visceral organs, since it is possible that stimulation of the abdominal visceral organs counteracts the effect of cutaneous stimulation. It is also possible that stroking the abdomen with a pressure of 80–100 mmH_2O becomes noxious (possibly due to visceral stimulation), since noxious stimulation with pinching of all the skin areas examined had no effect on DA release. In the present study, we did not examine the effects of tactile stimulation with lighter pressure of 15 mmH_2O to other skin areas including the back, forelimb, and hindlimb; thus, there is a possibility that lighter pressure may produce larger responses in DA release.

We have previously shown that noxious mechanical stimulation (pinching) of the skin in anesthetized rats increases the release of acetylcholine, noradrenaline, and serotonin in the cerebral cortex [32, 33], while innocuous mechanical stimulation (brushing) produces smaller increases in the release of acetylcholine in the cerebral cortex and has negligible effects on the release of noradrenaline and serotonin [32]. In contrast, the present study shows that DA release in the NAc increases in response to innocuous mechanical stimulation, but not by noxious mechanical stimulation. The specific excitatory effects of innocuous mechanical stimulation on DA release in the NAc probably relate to the functional role of this nucleus as a relay in the brain reward system. The fact that noxious mechanical stimulation had no effects on DA release in the NAc suggests that: (1) there is no projection to the VTA or NAc from the noxious mechanical afferent pathways or (2) there is some specific mechanism that inhibits noxious mechanical inputs reaching the VTA or NAc. In this context, one should note that the k-opioidergic system or the μ-opioidergic system suppresses DA release in the NAc in animal models of inflammatory or neuropathic pain [34, 35]. Further experiments are needed to clarify the reason why noxious pinching stimulation had no effect on DA release in the NAc in the present study.

Tactile stimulation elicits conscious perception and emotion, and in turn these can modulate DA release in the NAc, suggesting that the DA responses may be different between anesthetized and conscious animals. However, we

showed that DA release in the NAc is increased in conscious and anesthetized animals. This result suggests that tactile stimulation can initially influence DA release in the NAc without a major contribution from emotion or conscious perception. That is, this implies that the higher brain areas, which are thought to be easily suppressed by anesthesia, have no major inhibitory influence on the release of DA in the NAc in response to tactile stimulation. This is further supported by the fact that the DA responses in the naïve and habituated animals were similar. However, the increased secretion of DA with tactile stimulation in the conscious animals lasted longer than that observed in the anesthetized animals. The longer responses in the conscious animals may be related to behavioral changes or to stress produced by the stimulation. In agreement with the present results in the conscious animals, DA release in the NAc in response to stressful stimuli was observed only after the cessation of stimulation, but not during the stimulus period [36]. The PVT is one of the nuclei involved in eliciting the arousal state, and sensory stimulation, such as tactile stimulation, causes arousal in the conscious state. Therefore, the glutaminergic neurons originating in the PVT may also participate in the increased DA release in the NAc of the conscious animals by stimulating dopaminergic neuronal terminals [31].

In conclusion, the main finding of our study is that DA release in the NAc is increased by tactile cutaneous stimulation, but not by noxious cutaneous stimulation. These results underlie the clinical effects of tactile stimulation on anxiety and depression, and provide strong evidence that touch therapy is useful for relieving anxiety and depression. Further study is required to investigate the mechanism of DA release in the NAc to tactile stimulation in more detail.

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