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Brain Research 1016 (2004) 255–262

BRAIN RESEARCH

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Research report

Music improves dopaminergic neurotransmission: demonstration based on the effect of music on blood pressure regulation

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Accepted 3 May 2004
Available online 19 June 2004

Abstract

The mechanism by which music modifies brain function is not clear. Clinical findings indicate that music reduces blood pressure in various patients. We investigated the effect of music on blood pressure in spontaneously hypertensive rats (SHR). Previous studies indicated that calcium increases brain dopamine (DA) synthesis through a calmodulin (CaM)-dependent system. Increased DA levels reduce blood pressure in SHR. In this study, we examined the effects of music on this pathway. Systolic blood pressure in SHR was reduced by exposure to Mozart's music (K.205), and the effect vanished when this pathway was inhibited. Exposure to music also significantly increased serum calcium levels and neostriatal DA levels. These results suggest that music leads to increased calcium/CaM-dependent DA synthesis in the brain, thus causing a reduction in blood pressure. Music might regulate and/or affect various brain functions through dopaminergic neurotransmission, and might therefore be effective for rectification of symptoms in various diseases that involve DA dysfunction.
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Theme: Neurotransmitters, modulators, transporters, and receptors
Topic: Catecholamines

Keywords: Calcium/calmodulin-dependent dopamine synthesis; Music; Spontaneously hypertensive rat; Systolic blood pressure; Neostriatum; Dopamine dysfunction

1. Introduction

Music has a long history of healing physical and mental illnesses. Many clinical findings indicate that music reduces blood pressure in various patients [3,8,29,49,50] and attenuates symptoms in various types of diseases, such as epilepsy [10,30], Parkinson's disease (PD) [13,21], senile dementia [6,13,14,18], and attention-deficit/hyperactivity disorder (ADHD) [1]. The mechanism by which music modifies brain function, however, is not clear.

Since the 1980s, in vitro studies have suggested that tyrosine hydroxylase (TH), the rate-limiting enzyme for catecholamine synthesis, activity is regulated by calcium through a calmodulin (CaM)-dependent phosphorylation process [4,5,48]. The role of calcium in dopamine (DA) synthesis has been confirmed in vivo using new methods, such as ethanol-dependent behavior and brain mapping analysis for quantitative distribution of neurochemicals [36,37,40,47]. These findings indicate that peripheral calcium is transported to the brain via the blood, thereby enhancing CaM activity, and the CaM-dependent system subsequently increases DA synthesis in specific brain regions, i.e., neostriatum and nucleus accumbens, through the phosphorylation of TH [32,35].

Our hypothesis of the mechanism by which calcium regulates blood pressure is as follows [32]. Calcium ions have two separate roles in the regulation of blood pressure both centrally and peripherally. Namely, calcium increases blood pressure through an intracellular, calcium-dependent mechanism in the peripheral vasculature and reduces blood pressure through a central, calcium/CaM-dependent DA-synthesizing system. Acute and excessive increase in blood calcium levels, due to an infusion of calcium, hyperparathyroidism, or vitamin D toxicity leads to hypercalcemia. Increased calcium directly stimulates vascular smooth muscles and quickly elevates blood pressure. On the other

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doi:10.1016/j.brainres.2004.05.018

hand, when blood calcium levels are increased chronically and slightly by diet supplementation, hypercalcemia does not occur and calcium is transported to the brain. Subsequently, calcium activates DA synthesis in the brain and enhances dopaminergic (DAergic) activity, which inhibits sympathetic nerve activity. Thus, blood pressure is decreased by calcium. The low serum calcium levels in spontaneously hypertensive rats (SHR) might result from a decrease in the availability of bone calcium, which causes a decrease in DA synthesis in the brain, with the low level of brain DA producing an increase in blood pressure [43]. Thus, hypertension in SHR can be rectified by intracerebroventricular (i.c.v.) administration of calcium or DA [32,33].

This study investigated the effect of music on brain function through the calcium-dependent DA-synthesizing pathway.

2. Materials and methods

2.1. Animals

Male SHR (12 weeks of age) were purchased from Charles River Japan, (Kanagawa, Japan). The animals were housed at room temperature (22 ± 2 °C) in our animal center for 1 week before use in the experiments and exposed to a 12-h light/dark schedule. Food and water were provided ad libitum. A stainless steel cannula was stereotaxically implanted into the lateral cerebral ventricle. The experiments were performed in conscious rats 4 days after the cannula was implanted. Before the final experiment, systolic blood pressure was measured in all rats for 3 days to allow them to adapt to the measuring environment and to confirm original values. The animals were placed in a closed cage equipped with a speaker, and taped music (average sound level was 65 dB, peak level 75 dB) was played. Mozart, Adagio from Divertimento No. 7 in D Major, K. 205 were played repeatedly for 120 min, from 1800 to 2000 h. During and after music treatment, changes in blood pressure were analyzed. SHR in the nonmusic group were placed in the normal housing area (average room noise 35 dB). Animals received humane care in compliance with the "Guiding Principles for the Care and Use of Laboratory Animals" formulated by the Japanese Pharmacological Society.

2.2. Measurement of blood pressure

Systolic blood pressure was determined in conscious, warmed, and restrained rats using the tail–cuff method, with a programmed sphygmomanometer (BP-98A; Softron, Tokyo, Japan). The animals were restrained for 5 min using a temperature-controlled warming holder (37 °C) designed for rats, and systolic blood pressure was measured. Each estimation was the average of three recordings taken at 1-min intervals. First, the effects of music on systolic blood pressure in SHR was investigated. Next, the systolic blood pressure response in SHR elicited by music was compared among groups of animals pretreated with test substances as follows: SHR that were exposed to music for 120 min were injected i.c.v. with (a) physiologic saline 5 min before music; (b) W-7 (CaM antagonist, 30 μg/rat) 5 min before music; (c) EDTA (calcium chelator, 1 nmol/rat) 5 min before music; (d) α-methyltyrosine (αMPT, TH inhibitor, 1 mg/rat) 30 min before music; (e) SCH 23390 (DA D_1 receptor antagonist, 30 μg/rat) 15 min before music; and (f) eticlopride (DA D_2 receptor antagonist, 100 μg/rat) 15 min before music. SHR without music exposure were also injected i.c.v. with saline, W-7, EDTA, αMPT, SCH 23390, or eticlopride, and systolic blood pressure was measured. All substances were dissolved in saline. The dosages and injection conditions were determined by preliminary experiments based on previous reports [2,33,34,38]. The drugs were administered to conscious animals, using an injection volume of 10 μl/rat. Data were analyzed using Student's *t*-test for comparison of music and nonmusic groups. Also, data for the same period were analyzed using ANOVA with Dunnett's *t*-test for comparisons of multiple groups.

2.3. Measurement of serum calcium

Serum calcium levels were measured according to a method employing *o*-cresolphthalein complexone [25]. The calcium levels in SHR exposed to music for 15, 30, 60, or 120 min and the level in nonmusic control animals were compared. Blood were collected from each animal, and the serum was quickly separated and assayed. Data were analyzed using the analysis of variance (ANOVA) and Dunnett's *t*-test for multiple comparisons between each music group and the control group.

2.4. Measurement of brain DA levels

Brain DA levels in SHR exposed to music were compared with those of nonmusic control animals using quantitative immunohistochemical methods. The two groups (10 rats/group), i.e., nonmusic control SHR, and SHR exposed to music for 120 min, were prepared. Immediately after the termination of the music, the rats were anesthetized and perfused intracardially with 500 ml of a solution of 0.1 M cacodylate and 1% sodium metabisulfite containing 2.5% glutaraldehyde (pH 7.5). Whole brains were removed and postfixed in the same solution for 30 min, then frozen on dry ice. The frozen brains were sectioned coronally at 20-μm thickness in a cryostat. Brain sections approximately 8.4 mm rostral from the interaural line were chosen (Fig. 5), because these largely contain the neostriatum region, which has increased DA levels following i.c.v. administration of calcium chloride [40] and during exercise [31].

The immunohistochemical staining procedure was performed according to previous reports [31,40]. The DA antibody [7] was a gift from Dr. M. Geffard (University of Bordeaux II, France). Immunohistochemical distribution of

DA was quantitatively analyzed using a brain mapping analyzer [46]. This analyzer measures the distribution of immunohistochemical fluorescence intensity in a tissue slice. Average fluorescence intensity in a small brain region is measured using a photomultiplier tube through a pinhole and objective of a microscope. The brain slice is continuously moved in the *x*- or *y*-direction using a scanning stage under the objective lens, and data for each brain region are collected. An excitation filter of 420 to 490 nm and an interference filter of 530 nm were used. The brain slices were measured at 20-μm intervals through a 6-μm diameter field. Background values, such as nonspecific fluorescence originating from glutaraldehyde, were subtracted photometrically from the total fluorescence intensity value at each measuring point [44]. Pure immunohistochemical fluorescence intensities relative to standard 1 mM quinine sulphate [46] were classified into eight ranks and were indicated by color coding. The average fluorescence intensity in each region was obtained from 20 slices, 2 slices in each of 10 brains per group, and analyzed by Student's *t*-test for comparison of the two groups.

3. Results

3.1. Effect of music on hypertension

First, we analyzed the effect of music on hypertension in SHR to confirm that music modifies brain function. Systolic blood pressure in SHR decreased significantly during exposure to music and after cessation of the music. Systolic blood pressure decreased gradually after the start of the music exposure period; the decrease lasted for at least 30 min postmusic exposure, and then returned gradually to the premusic level. The blood pressure levels in SHR at 30 to 120 min after starting the music and 0 to 120 min after the cessation of music were lower by 13 to 24 mmHg ($P<0.05-0.001$) than the nonmusic control level (Fig. 1).

Next, to confirm whether the effect of music occurs via calcium and DA dependent system in brain, the effects of i.c.v. pretreatment with various drugs on the music-dependent response of blood pressure were analyzed. In SHR without exposure to the music, systolic blood pressure was not significantly affected by i.c.v. treatment with W-7, EDTA, αMPT, SCH 23390, or eticlopride (data not shown). The baseline levels of systolic blood pressure in animals pretreated i.c.v. with these drugs were equal to the levels in saline-treated SHR. On the other hand, the music-induced depressor response during music and postmusic exposure periods was significantly inhibited by i.c.v. pretreatment with W-7, EDTA, or αMPT compared to the saline-treated group (Fig. 2). In addition, the depressor response elicited by music exposure was inhibited by i.c.v. pretreatment with the D_2 receptor antagonist eticlopride, but not by the D_1 receptor antagonist SCH 23390 (Fig. 3).

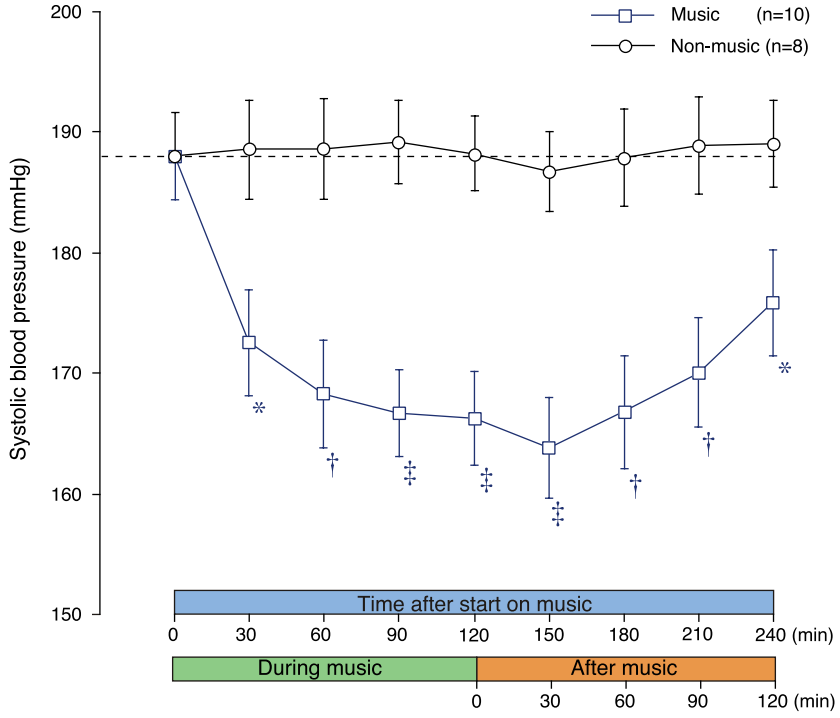

Fig. 1. Music-dependent change in systolic blood pressure in SHR. Systolic blood pressure decreased significantly during and after exposure to music, for a minimum of 30 min postmusic, and then returned gradually toward baseline. A significant hypotensive response was maintained for 120 min after cessation of the music. Results are expressed as mean ± S.E.M. Dotted line indicates the premusic level. *$P<0.05$, †$P<0.01$, ‡$P<0.001$ compared to the nonmusic group by Student's *t*-test.

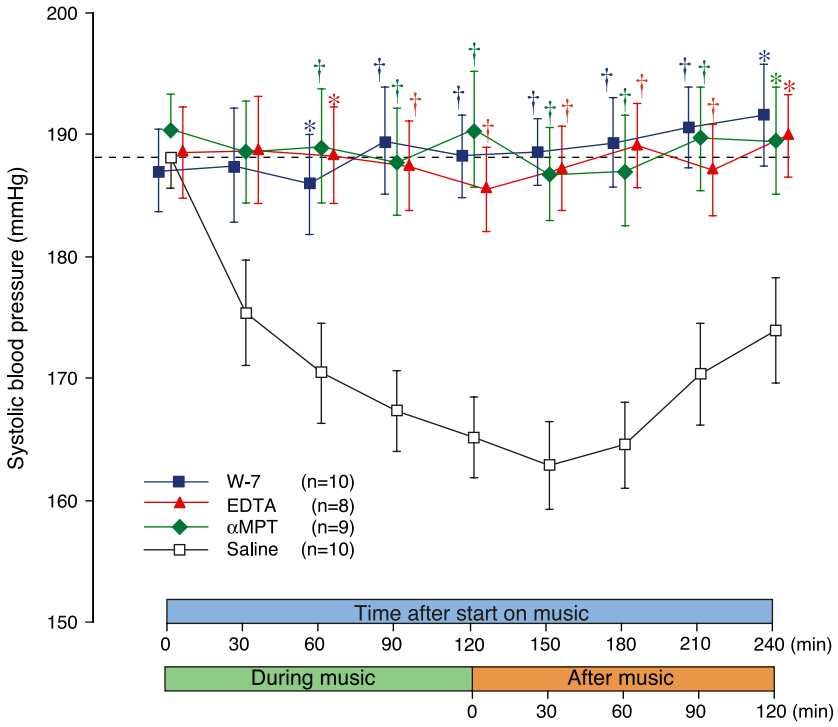

Fig. 2. The effects of various drugs on the response of the systolic blood pressure elicited by music in SHR. Time-course of the systolic blood pressure in SHR pretreated i.c.v. with saline, W-7, EDTA, or αMPT during and after music exposure. The i.c.v. administration of W-7, EDTA, or αMPT inhibited the decrease in systolic blood pressure elicited by music. Results are expressed as mean ± S.E.M. *$P<0.05$, †$P<0.01$ compared with saline-treated group by Dunnett's *t*-test.

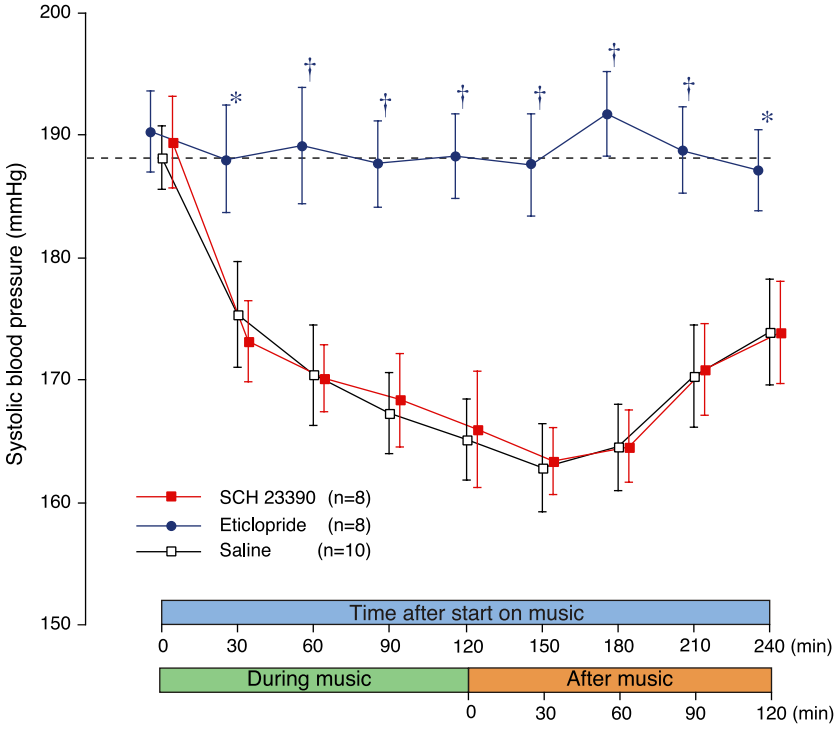

Fig. 3. The effects of DA antagonists on the response of the systolic blood pressure elicited by music in SHR. Time-course of the systolic blood pressure in SHR pretreated i.c.v. with saline, SCH 23390, or eticlopride during and after music exposure. The i.c.v. administration of eticlopride, but not SCH 23390, inhibited the decrease in systolic blood pressure elicited by music. Results are expressed as mean ± S.E.M. *$P<0.05$, †$P<0.01$ compared with saline-treated group by Dunnett's *t*-test.

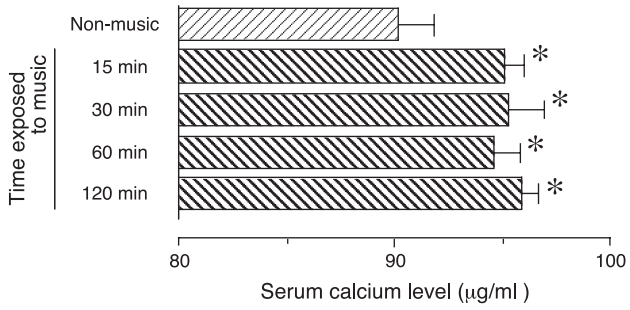

Fig. 4. Effect of music on serum calcium level in SHR. The five groups (8–10 rats/group), i.e., nonmusic control SHR and SHR exposed to music for 15, 30, 60, or 120 min, were analyzed. The serum calcium levels increased during exposure to music. Results are expressed as mean ± S.E.M. *$P<0.05$ compared to the nonmusic group by Dunnett's t-test.

3.2. Effect of music on serum calcium levels

The effect of music on the serum calcium levels in SHR was confirmed biochemically. As shown in Fig. 4, increases in the serum calcium level were noted during music exposure. The serum calcium level increased slightly, and then kept its level during music exposure. The calcium levels in SHR exposed to music for 15 to 120 min were 5–6% ($P<0.05$) higher than that in the nonmusic control animals.

3.3. Effect of music on brain DA levels

Effect of music on the brain DA levels in SHR was confirmed using the brain-mapping analyzer. The neostriatum had the highest immunohistochemical fluorescence intensity of DA in nonmusic control SHR. The mean ± S.E.M. of the fluorescence intensity in the lateral area of the neostriatum was 0.451 ± 0.021. In this region, the DA levels were increased by exposure to the music. The fluorescence intensity of DA in the lateral area of the neostriatum in SHR who were exposed to music for 120 min was 18% higher ($P<0.01$) than that in the brains of the control SHR (Fig. 5; Table 1). The DA levels in other analyzed regions were not significantly changed by exposure to the music.

4. Discussion

Our previous animal experiments suggested that peripheral calcium is transported to the brain where it leads to increased brain DA levels, which in turn improve DAergic neurotransmission in some diseases, such as hypertension or epilepsy [32,42]. For example, blood pressure in rats is reduced following i.c.v. administration of calcium chloride, and this effect of calcium is attenuated by W-7, EDTA, αMPT, hexamethonium (autonomic ganglion blocker), or eticlopride, but not by SCH 23390 [32,33,38]. In addition, i.c.v. injection of DA produces a decrease in blood pressure in rats [32,38]. These studies indicate that calcium enhances DA synthesis in the brain through a CaM-dependent system, and that the resultant increase in DA levels inhibits sympathetic activity via D_2 receptors and reduces blood pressure. Ingested calcium or serum calcium is transported to the brain, which reduces blood pressure through this system [32,39,41,45].

In this study, systolic blood pressure in SHR was significantly reduced along with decreased behavioral activity during and after exposure to Mozart's music. The effect of music on blood pressure in SHR vanished following inhibi-

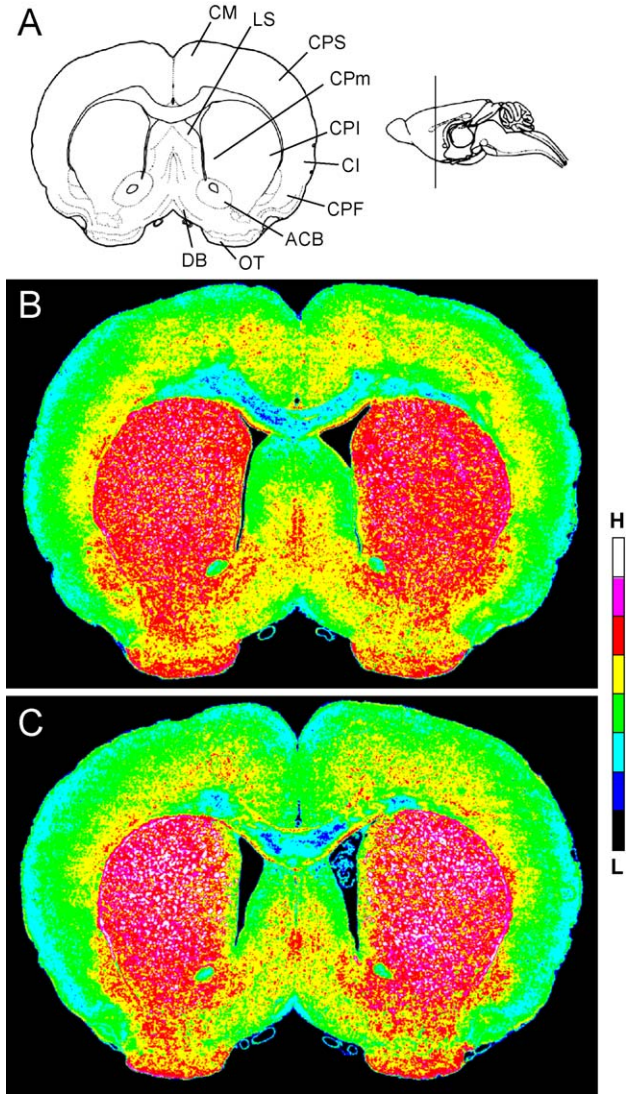

Fig. 5. Effect of music on the immunohistochemical DA distribution in the brain of SHR. (A) A coronal section, approximately 8.4 mm rostral from the interaural line, analyzed at 20-μm intervals using a brain mapping analyzer. ACB, nucleus accumbens; CI, insular cortex; CM, motor cortex; CPF, piriform cortex; CPl, lateral area of neostriatum; CPm, medial area of neostriatum; CPS, primary somatosensory cortex; DB, diagonal band; LS, lateral septal nucleus; OT, olfactory tubercle. (B and C) Examples of the quantitative distribution of DA in nonmusic control SHR (B) and SHR which received music for 120 min (C). Immunohistochemical fluorescence intensities were classified into eight ranks and are indicated by color coding. The DA levels in the lateral area of the neostriatum of SHR which received music were significantly higher than those in control animals.

Table 1
Effect of music on the immunohistochemical DA levels in various brain regions of SHR

Brain region	Fluorescence intensity (measured value × 10)	
	Nonmusic	Music
Motor cortex	0.76 ± 0.09	0.79 ± 0.12
Primary somatosensory cortex	0.69 ± 0.12	0.74 ± 0.08
Insular cortex	0.64 ± 0.13	0.74 ± 0.12
Piriform cortex	0.64 ± 0.14	0.62 ± 0.11
Neostriatum (lateral)	4.51 ± 0.21	5.31 ± 0.16*
Neostriatum (medial)	4.17 ± 0.18	4.50 ± 0.19
Nucleus accumbens	3.77 ± 0.14	3.92 ± 0.18
Olfactory tubercle	3.38 ± 0.25	3.48 ± 0.15
Lateral septal nucleus	0.66 ± 0.10	0.67 ± 0.11
Diagonal band	0.69 ± 0.10	0.70 ± 0.09

The immunohistochemical fluorescence intensities of DA in the brain are shown for the nonmusic control SHR, and SHR exposed to music for 120 min. These data were obtained at random from each brain region, which is indicated in Fig. 5. Each value represents the mean ± S.E.M. of 20 slices (two slices in each of 10 brains).

*$P < 0.01$ compared to nonmusic group by the Student's *t*-test.

tion of the calcium-dependent DA-synthesizing pathway in the brain by injection of W-7, EDTA, or αMPT. This effect of music also vanished by pretreatment with a D_2 antagonist, but not by a D_1 antagonist. In addition, serum calcium levels and DA levels in the neostriatum were significantly increased by music. Together these results with the findings of previous studies suggest that music leads to an increase in calcium/CaM-dependent DA synthesis in the brain, and that the subsequent increase in DA reduces blood pressure via D_2 receptors. Acceleration of calcium-dependent DA synthesis might thus be a mechanism by which music modifies blood pressure and other brain functions. Consistent with these findings, Panksepp and Bernatzky [23] reported that musical stimulation increases brain DA levels and homovanillic acid levels, a DA metabolite, in young chicks.

On the basis of these findings, we hypothesize that music is effective for rectification of symptoms in various diseases that involve DA dysfunction. The loss of striatal DA accounts for most of the symptoms in PD, and treatment with L-DOPA, the immediate precursor of DA, improves some symptoms in PD [12]. Therefore, some symptoms of PD might be rectified by music through increased calcium-dependent DA synthesis. Several studies have examined the effect of music therapy on symptoms of PD, and their clinical findings support this hypothesis [13,21]. Pacchetti et al. [21] reported a significant improvement in motor function, emotional function, and activities of daily living after music therapy. It is possible that music increases DA synthesis in the remaining DAergic nerve cells in the neostriatum and eases some symptoms of PD. In addition to PD, abnormally reduced neostriatal DAergic function has also been reported in epilepsy [9,42], dementia with Lewy bodies [15,24], or ADHD cases [20]. Thus, music might attenuate symptoms of these diseases, and has been reported to rectify the symptoms of epilepsy [10,30], dementia [6,13,14,18], and ADHD [1].

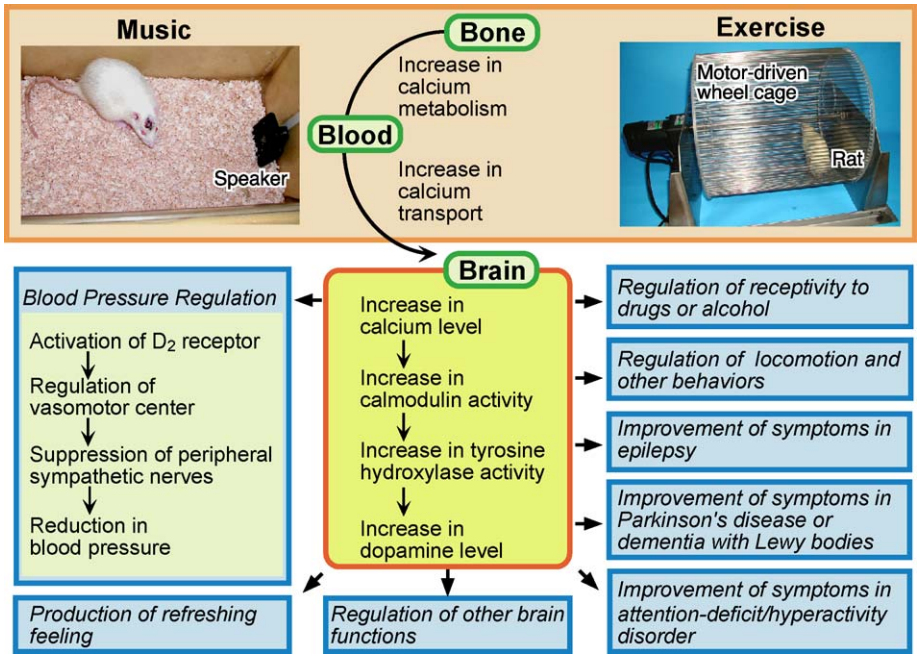

Fig. 6. Possible physiologic sequence induced by music. Music leads to an increase in serum calcium levels, which is transported to the brain and in turn leads to an increase in DA synthesis, and the subsequent increase in DA reduces blood pressure via D_2 receptor. Previous studies suggest that exercise also stimulates this pathway [35]. Stimulated pathway regulates various functions with reduce in blood pressure. This pathway also might ease the symptoms in epilepsy, PD, dementia with Lewy bodies, or ADHD, because in these diseases, DAergic neurotransmission is abnormally reduced. We think that the acceleration of calcium-dependent DA synthesis is a mechanism by which music or exercise modifies brain functions, and that the activities of daily life, such as music and exercise, are very important for the maintenance of normal brain function.

Previous reports demonstrate that exercise stimulates the calcium metabolic hormone [16,28] and increases blood calcium levels [31], thereby increasing DA synthesis in the brain [31,35], similar to the effect of music. Thus, systolic blood pressure in SHR was reduced following exercise [2]. The effect of exercise on blood pressure in SHR was inhibited by pretreatment with EDTA, αMPT, or D_2 receptor antagonists [2]. In addition, some symptoms of PD or senile dementia are improved by exercise [11,17,19,22,26,27], and symptoms of epilepsy are improved by convulsions that have some resemblance to exercise with respect to movement [35,42]. We think that the activities of daily life, such as music, exercise, or slight stress, enhance DAergic activity, and therefore subsequently regulate and/or affect various brain functions, and that this mechanism might underlie the improving effect of the activities of daily living on the symptoms in various diseases that involve DA dysfunction (Fig. 6).

Acknowledgements

We wish to express our thanks to Mr. Tsuneo Watanabe, the president of the Yomiuri Shimbun (Japanese newspaper), who kindly gave us encouragement throughout our study.

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