Effects of Nonpharmacological Therapies for Diseases of the Elderly

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Adverse events are a concerning issue related to pharmacotherapy for the elderly. Therefore, we investigated nonpharmacological therapy for diseases of the elderly, which cause fewer adverse events compared with those caused by appropriate pharmacotherapy. The effects of each treatment were examined using the PC12m3 cell line before clinical study. This cell line comprises mutant cells of the PC12 model neuronal cell line. Treatments from which an effect was expected were clinically studied. VAT (vibroacoustic therapy) provided relaxation effects for elderly nursing home residents and improved depressive symptoms. Steam foot spa treatment resulted in improved cognitive function in geriatric inpatients and a temporary decrease in high blood pressure. The effect of bright light therapy was assessed using PC12m3 cells, and the results were promising for clinical study. However, we did not conduct clinical research because ultraviolet rays were considered to be one of the factors causing the effect.

Keywords: PC12m3 cell, VAT (vibroacoustic therapy), steam foot spa treatment, BLT (bright light therapy)

Effects of VAT (Vibroacoustic Therapy)

Effects on PC12m3 cells

The PC12m3 cell line is a mutant cell line derived from the neuronal model cell line, PC12, developed by Greene (1977). PC12m3 cells exhibit poor neurite outgrowth in response to NGF (nerve growth factor). Cells treated with NGF show enhanced neurite outgrowth in response to various stimuli such as calcium ionophore, the FK506 immunosuppressant, and heat shock (Kano et al., 2002).

Results. In our study (Koike, 2004), PC12m3 cells were exposed to vibratory sound stimuli at frequencies of 10-200 Hz for 30 min, followed by treatment with NGF. The results showed that low-frequency vibratory sounds of 20-100 Hz enhanced neurite outgrowth. The frequency of neurite outgrowth induced by 40-Hz, low-frequency, vibratory sound stimuli was approximately three-fold greater than that induced by NGF alone. Activation of p38 MAPK (mitogen-activated protein kinase) plays an important role in neuronal differentiation of PC12m3 cells. Therefore, we examined whether the ability of a low-frequency vibratory sound stimulus to induce neurite outgrowth of PC12m3 cells is a reflection of its effect on p38 MAPK activity. The results showed that vibratory sound induced neurite outgrowth via the p38 MAPK signaling pathway in PC12m3 cells.

VAT

VAT, which was proposed by Skill (1989) in 1989, is attracting increasing attention for its therapeutic

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effects. VAT may be a professional challenge for music therapy. Most of its effects are found in the 40-80-Hz range, which is the range in the very center of the vibroacoustic area. In VAT, vibrations are applied directly to the body in the form of low-frequency sinusoid tones in combination with selected music.

Standly (1991) reported that VAT, which combines listening to music with vibrotactile stimulation, results in deeper relaxation effects compared with listening to music alone. In addition, Lundquist, Anderson, and Viding (2009) reported that VAT effectively decreases self-injurious, stereotypic, and destructive behavior among individuals with developmental disabilities.

Clinical Use of VAT

In our study (Koike, Hoshitani, Tabata, Seki, Nishimura, & Kano, 2012), VAT provided relaxation effects for elderly nursing home residents and improved depressive symptoms.

Subjects and methods. Fifteen elderly NH (nursing home) residents (five men, 10 women; 86.3 ± 7.8 years) with surface psychological symptoms of depression were included. All 15 subjects underwent VAT for 30 min daily for two consecutive weeks, except Saturdays and Sundays.

Results. Depression was significantly ameliorated, as assessed by the DMAS (Dementia Mood Assessment Scale; $p < 0.05$). In addition, depression and sadness were significantly ameliorated, as assessed by items 1–17 of the DMAS ($p < 0.05$). Significant decreases ($p < 0.001$) in tympanic temperature and pulse rate were observed after VAT (see Table 1). The mean total sleep duration in the second week decreased significantly compared with that during the first week ($p < 0.05$). Furthermore, a significant increase in mean wake time was observed during the second week compared with that during the first week ($p < 0.05$) (see Table 2).

Table 1

Effect of VAT on Cognitive Function, Behavioral Symptoms, and Psychological Symptoms

	Before VAT (mean $\pm$ SD)	After VAT (mean $\pm$ SD)	<i>p</i> -value
MMSE	19.4 $\pm$ 7.21	19 $\pm$ 7.58	0.577
DBD	25.93 $\pm$ 10.45	25.26 $\pm$ 13.51	0.554
DMAS (total on 24 items)	49.66 $\pm$ 16.17	43.8 $\pm$ 17.93*	0.021
Overall dementia severity (DMAS; items 1-17)	36.66 $\pm$ 11.13	32.93 $\pm$ 14.05*	0.011
Depression and sadness (DMAS; items 18-24)	12.33 $\pm$ 7.22	10.86 $\pm$ 7.68	0.247
MMSE, Mini Mental State Exam; DBD, Dementia Behavior Disturbance scale; DMAS, Dementia Mood Assessment Scale			

Note. $n = 15$, * $p < 0.05$.

Table 2

Effect of VAT on Physiological Responses

	Before VAT (mean $\pm$ SD)	After VAT (mean $\pm$ SD)	<i>p</i> -value
Tympanic temperature ($^{\circ}$ C)	36.46 $\pm$ 0.47	36.31 $\pm$ 0.53***	0.00000134
SpO ₂ (%)	95.3 $\pm$ 2.5	95.08 $\pm$ 2.77	0.166
Pulse (beats/min)	72.28 $\pm$ 9.88	70.66 $\pm$ 9.44***	0.0000725
Blood pressure (systolic) (mmHg)	139.16 $\pm$ 24.96	138.56 $\pm$ 24.17	0.844
Blood pressure (diastolic) (mmHg)	73.04 $\pm$ 14.43	73.29 $\pm$ 14.81	0.751

Note. $n = 150$, *** $p < 0.001$.

Discussion. Blumenthal reported that aerobic exercise is an effective treatment for depression in the

elderly, with effects comparable to those of antidepressant drugs (Blumenthal, 1999). In studies on intracellular transduction pathways during aerobic exercise using mouse muscle cells, Akimoto reported that MKK3/MKK6 is activated in the MAPKK (mitogen-activated protein kinases kinase) pathway by aerobic exercise, leading to activation of downstream p38 α MAPK and, eventually, mitochondrial biosynthesis (Akimoto, 2005). In our previous studies in which the effects of low-frequency vibratory sound were investigated using the PC12m3 cell line, we found that MKK3/MKK6 in the MAPKK pathway was activated by low-frequency vibratory sounds of 20-100 Hz, leading to activation of p38 MAPK downstream in the MAPK pathway (Koike, 2004). Overall, these reports suggest that VAT stimulation has an effect similar to that of aerobic exercise by activating p38MAPK.

Falempin and In-Albon (1999) suggested that tendon vibration (120 Hz) in the rat soleus muscle can be used as a paradigm to counteract the atrophic process observed after hindlimb unloading. In addition, Skill reported that vibroacoustic music (40-80 Hz) decreases muscle tone and spasms (Skill, 1989). It is possible that the mitigation of depression by VAT in elderly NH residents in this study was caused by vibrotactile stimuli, which represents passive aerobic exercise.

Future well-controlled studies are required to confirm these findings.

Effect of a Steam Foot Spa

Effect on PC12m3 Cells

We investigated the role of the p38 MAPK pathway in heat shock-induced neurite outgrowth of PC12 mutant cells with impaired NGF-induced neurite outgrowth (Kano, 2002; Kano, 2001). When cultures of PC12m3 cells were exposed to heat stress at 44°C for 10 min, p38 MAPK activity increased and neurite outgrowth was enhanced (Kano, 2004). Neurite extension was inhibited by the p38 MAPK inhibitor SB203580. Longer heat treatment of PC12m3 cells provoked cell death, which was enhanced by SB203580. These findings suggest that heat-induced activation of p38 MAPK is responsible for neurite outgrowth and survival of PC12m3 cells.

In this study, the p38 MAPK pathway induced differentiation of PC12m3 cells because p38 MAPK was activated by heat shock at 44°C for 10 min; however, ERK and JNK were not activated under the same heat conditions. Furthermore, PC12m3 cells have poor neurite outgrowth despite normal sustained activation of ERK following NGF treatment. Cells respond to elevated temperature by activating p38 MAPK and JNK and by increasing the production of HSP (heat shock proteins) such as HSP27 and 70 as well as Akt (Mearow, Dodge, Rahimtula, & Yegappan, 2002; Quigney, Gorman, & Samali, 2003). One target of p38 MAPK is MAPKAP-K2, which phosphorylates HSP27. This, in turn, modulates both the chaperone activity and anti-apoptotic effects of HSP27 (Mearow et al., 2002). HSP70 protects cells from a number of apoptotic stimuli through its chaperone functions of protein folding and assembly (Samali & Cotter, 1996; J. S. Lee, J. J. Lee, & Seo, 2005). HSP70 also modulates stress-activated signaling by direct binding to JNK (Park, Lee, Huh, Seo, & Choi, 2001). Apoptosis was not observed when PC12m3 cells were exposed to heat shock at 44°C for 10 min, whereas cell death had already initiated under the same heat conditions in PC12 parental cells. These phenomena may depend on the strong activation of p38 MAPK and HSP following heat-shock treatment of PC12m3 cells.

Clinical Effect of Waon Therapy

Waon (“Wa” means soothing and “On” means warmth) therapy using an evenly maintained dry sauna

system at 60°C, which differs from a traditional sauna, has been studied exclusively by Tei in Japan (Miyachi et al., 2012; Kuwahata, 2011; Matsushita, Masuda, & Tei, 2007). Waon therapy warms the entire body in a uniformly heated chamber (60°C) for 15 min and maintains the soothing effect outside the sauna for an additional 30 min. Waon therapy is administered once a day (one session) for five days a week and is recommended for more than two weeks or as desired thereafter. Waon therapy has beneficial effects on peripheral arterial disease and is safe, beneficial, and well tolerated by patients with heart failure.

The vasodilator response due to direct heat is lost immediately during Waon therapy. However, cardiac output increases to increase peripheral blood flow, and shear stress occurs repeatedly in the peripheral vascular endothelium. This results in an increase in endothelial NO (nitric oxide) expression.

Waon Therapy for Hamsters

Fujita et al. (2011) examined the effects of a dry sauna on improvement in cardiac function using TO-2 cardiomyopathic hamsters. These hamsters were treated in a dry sauna system at 39°C for 15 min, and the soothing effect was maintained outside the sauna for an additional 20 min (30°C).

The results suggest that Waon therapy activated the p38 MAPK signaling pathway, leading to the induction HSP27, manganese superoxide dismutase, and HSP32. This induction decreased oxidative stress (4-hydroxy-2-nonenal) and led to improved cardiac function.

Steam Foot Bath in a Patient With CHF (Chronic Heart Failure)

Higashi, Komamura, and Oda (2009) provided 15-min steam foot baths and gloves heated to 42°C for two weeks to a 21-year-old male with severe CHF who required a left ventricular assist device, followed by 30 min of rest and heat retention in bed. They reported that appendicular thermal therapy was safe in this patient, who was waiting for a heart transplant, and that the procedure may be beneficial for patients with end-stage heart failure.

Clinical Effects of a Steam Foot Spa Treatment

The results of a VAT pilot study suggest that steam foot spas mitigate cognitive impairment in geriatric inpatients (Koike, H. Kondo, S. Kondo, Takagi, & Kano, 2013).

Subjects and methods. Geriatric inpatients (13 participants; age, 82.69 ± 6.53 years) with cognitive impairment (MMSE score: 18.38 ± 3.69) were given a 20-min steam foot spa treatment at 42°C for two weeks, five days a week. Physiological indicators such as blood pressure, percutaneous oxygen saturation, pulse, tympanic temperature, and sleep time and efficiency were assessed.

Cognitive function and behavioral and psychological symptoms of dementia were assessed using the MMSE (Mental State Examination), DMAS (Dementia Mood Assessment Scale), and Dementia Behavior Disturbance Scale.

Results. Systolic ($p < 0.01$) and diastolic blood pressure ($p < 0.05$) significantly decreased while tympanic temperature ($p < 0.01$) significantly increased after the steam foot spa compared with those before treatment. A significant improvement was observed in the MMSE score ($p < 0.01$) and in the overall scores for the dementia severity items on the DMAS ($p < 0.05$) (see Table 3).

Discussion. The cholinergic nervous system, which projects from the NBM (nucleus basalis of Meynert) in the basal forebrain to the cerebral cortex and from the septal region to the hippocampus, dilates the blood vessels in the cerebral cortex and hippocampus (Sato & Sato, 1992; Lacombe, Sercombe, Verrecchia, Philipson, MacKenzie, & Seylaz, 1989). Piché, Uchida, Hara, Aikawa, and Hotta (2010) increased NBM nerve activity

with somatosensory stimulation and found that acetylcholine is released and blood flow increases within the cerebral cortex. Activation of the nicotinic acetylcholine nervous system enhances the neuroprotective effect to promote increased NGF secretion (Hotta, Kagitani, Kond, & Uchida, 2009).

In this study, cerebral blood flow increased in geriatric inpatients with an increase in tympanic temperature caused by the steam foot spa treatments. A significant change in the MMSE was observed after the steam foot spa treatment. These results suggest that changes in the MMSE following steam foot spa treatments occurred because of vasodilation of cholinergic neurons.

Table 3

Effect of VAT on Sleep-Wake Rhythm

	First week (Mean $\pm$ SD)	Second week (Mean $\pm$ SD)	<i>p</i> -value
Total sleep time (min)	626.54 $\pm$ 221.35	599.61 $\pm$ 216.55*	0.0309
Nighttime sleep (min)	346.41 $\pm$ 174.21	347.8 $\pm$ 172.28	0.707
Nighttime sleep efficiency (%)	88.64 $\pm$ 8.33	89.28 $\pm$ 9.76	0.702
Wake time (min)	813.45 $\pm$ 221.35	838.06 $\pm$ 217.48*	0.0442

Note. $n = 75$, * $p < 0.05$.

A significant antihypertensive effect was observed in this pilot study. Although blood pressure decreased significantly after 20 min of treatment, heart rate did not change. Cholinergic nerves cause vasodilation; however, there was no sustained excitability of these nerves. Therefore, no change in heart rate variability was observed.

The vasodilator response to direct heat is lost immediately during Waon therapy. However, cardiac output increased to increase the peripheral blood flow, and shear stress occurred repeatedly in the peripheral vascular endothelium. As a result, the expression of NO in the endothelium increased.

These results suggest that steam foot spa treatments at an ideal setting of 42°C for 20 min potentially improve cognitive function in elderly hospitalized patients with mild to moderate cognitive impairment. In addition, it may lead to improved cardiac function.

BLT (Bright Light Therapy)

BLT

An obvious initial candidate for BLT is a patient with seasonal affective disorder (winter depression) (Rosenthal, 1984; James, Wehr, Sack, Parry, & Rosenthal, 1985). The efficacy of BLT has been supported across a range of mood disorders, including nonseasonal depression and chronic depression (Golden et al., 2005; Kripke, 1998; Goel, Terman, Terman, Macchi, & Stewart, 2005), manic-depressive psychosis (Deltito, Moline, Pollak, Martin, & Maremmanni, 1991; Sit, Wisner, & Hanusa, 2007), antepartum and postpartum depression (Oren, Wisner, & Spinelli, 2002; Wirz-Justice, 2011). Moreover, BLT improves disturbances and insomnia caused by Alzheimer's disease (Ancoli-Israel, Martin, Kripke, Marler, & Klauber, 2002; Nowak & Davis, 2011). BLT is usually administered at ≥ 2500 lux. Although no direct studies comparing different light intensities have been conducted, longer exposure (approximately 2-3 hours) at 2,500 lux or shorter exposure (about 30 min) at higher intensities such as 10,000 lux is recommended (Young, 2011).

Effects of UVC Irradiation on PC12m3 Cells

We have previously investigated cellular damage and differentiation of PC12m3 cells caused by UVC

irradiation (Koike et al., 2006). When PC12m3 cells are exposed to UVC irradiation, the frequency of neurite outgrowth rapidly increases in a dose-dependent manner. The frequency of neurite outgrowth was maximized at 40 J/m² of UVC irradiation. The frequency of neurite outgrowth induced by 40 J/m² of UVC irradiation was approximately 25-fold greater than that of neurite outgrowth induced by NGF alone. However, PC12m3 cell survival was inversely proportional to the dose of UVC irradiation.

We examined whether a UVC irradiation stimulus to induce neurite outgrowth of PC12m3 cells is a reflection of its effect on p38 MAPK activity. The results showed that p38 MAPK was strongly activated, whereas JNK and ERK were only weakly activated in PC12m3 cells exposed to UVC. Furthermore, UVC irradiation rapidly and strongly activated cAMP response element-binding in PC12m3 cells.

Bright Light Energy

Fluorescent light provides a source of UVC. UVC usually does not pass through glass, except quartz glass. However, a very small quantity of UVC leaks from a fluorescent tube.

In our preliminary research (date not shown), PC12m3 cells were exposed to a 15,000-lux bright light device at a distance of approximately 15 cm for 10 min. Then, one group of cells was removed from the UVC and another group of cells was continually exposed. The result showed that when PC12m3 cells were exposed to UVC irradiation, the frequency of neurite outgrowth was significantly higher than that in the group that was not exposed to UVC ($p < 0.05$).

Conclusions

This was a preliminary study, and we did not conduct a clinical study because UVC is considered to be a factor that affects the BLT effect.

Future Directions

With regard to the effectiveness of these nonpharmacological treatments presented on this occasion, these researches itself have not gone beyond the scope of preparatory researches, and the effectiveness of these treatments have not yet reached the stage where it can be guaranteed. Thus, it is necessary to acquire further proof of effectiveness through clinical trials.

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