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H. 知的財産権の出願・登録状況

1. 特許取得
なし
2. 実用新案登録
なし
3. その他
なし

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yanaga A., Goto H., Nakagawa T. Hikiami H., Shibahara N. and Shimada Y.	Cinnamaldehyde Induces Endothelium-dependent and -independent Vasorelaxant Action on Isolated Rat Aorta.	BIOLOGICAL & PHARMACEUTICAL BULLETIN	29	2415-2418	2006
Oguro H. Yamaguchi S. Abe S. Ishida Y. Bokura H. Kobayashi S.	Differentiating Alzheimer's disease from subcortical vascular dementia with the FAB test.	Journal of Neurology	253	1490-1494	2006
小林祥泰	アパシー（意欲低下）と認知機能	認知神経科学	8	165-168	2006

Cinnamaldehyde Induces Endothelium-Dependent and -Independent Vasorelaxant Action on Isolated Rat Aorta

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The vasorelaxant effect of cinnamaldehyde, one of the major oil components in Cinnamomi Cortex, was studied using isolated rat aorta. Cinnamaldehyde at final concentrations of 1 μM to 1 mM showed dose-dependent relaxation of the rat aorta contracted by treatment with prostaglandin $F_{2\alpha}$, norepinephrine or KCl. In addition, cinnamaldehyde relaxed prostaglandin $F_{2\alpha}$-precontracted aortic rings with endothelium and without endothelium, with the latter being significantly less sensitive than the former. Relaxation induced by cinnamaldehyde with endothelium was significantly inhibited by N^G-nitro-L-arginine methyl ester (L-NAME), while nonselective cyclooxygenase inhibitor (indomethacin), β-adrenergic receptor blocker (propranolol), an inhibitor of phosphodiesterase (theophylline), a delayed rectifier K^+ channel blocker (tetraethyl ammonium chloride), or an ATP-sensitive K^+ channel blocker (glibenclamide) did not reduce the relaxation induced by cinnamaldehyde with endothelium treated by L-NAME. Conversely, aorta pretreatment with L-NAME and theophylline increased the relaxation by cinnamaldehyde significantly compared to aorta pretreatment with only L-NAME. Furthermore, cinnamaldehyde significantly inhibited Ca^{2+}-induced contraction. These results suggested that the vasorelaxant effects of cinnamaldehyde were derived from both endothelium-dependent and -independent effects. Endothelium-dependent relaxation is affected by nitric oxide, and one of the mechanisms of endothelium-independent relaxation is thought to be influenced by the blocking of Ca^{2+} channels.

Key words cinnamaldehyde; endothelium-dependent relaxation; nitric oxide; endothelium-independent relaxation; theophylline; rat aorta

Cinnamomi Cortex is a crude drug used therapeutically in Asia and Europe. Its main component is cinnamaldehyde. There are many reports on the pharmacological effects of Cinnamomi Cortex. Mainly, the sedative effect of decreasing spontaneous motor activity,[1] anti-inflammatory effects related to cyclooxygenase-2,[2] and antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa*[3] have been reported. In addition, in oriental medicine, Cinnamomi Cortex is often used to improve blood circulation. In regard to the circulatory system, a catecholamine-releasing effect of cinnamaldehyde,[4] a reducing effect on platelet aggregation due to suppression of the release of arachidonic acid from platelets,[5] and an inhibitory effect of collagen-induced platelet aggregation[6] have been reported. However, reports concerning the direct effect against vasomotion by components of Cinnamomi Cortex are few, except in relation to cinnamtannin.[7] In the present study, the vasorelaxant effects of cinnamaldehyde were studied by the organ bath method, and the mechanisms of vasorelaxation were evaluated.

MATERIALS AND METHODS

Drugs and Chemicals Analytical grades of the following reagents were purchased: cinnamaldehyde, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), norepinephrine (NE), acetylcholine, sodium nitroprusside dehydrate (SNP), methylene blue trihydrate, theophylline, propranolol hydrochloride, indometacin, tetraethylammonium chloride (TEA), glibenclamide and verapamil hydrochloride, all from Wako Pure Chemical Ind. Ltd. (Osaka, Japan). N^G-nitro-L-arginine methylester (L-NAME) was from Sigma (St. Louis, MO, U.S.A.) and pentobarbital sodium salt was from Tokyo Chemical Ind. (Tokyo, Japan).

Animals Male Wistar rats weighing 370—420 g were purchased from Japan SLC (Shizuoka, Japan). They were kept in an animal room at an ambient temperature of 23±1 °C under a 12-h dark–light cycle. Experimental protocols met the "Guidelines for Animal Experimentation" approved by the Japanese Association of Laboratory Animal Science and the Japanese Pharmacological Society.

Preparation of Rat Aorta Rats were anesthetized (50 mg/kg i.p. pentobarbital) and sacrificed by cutting their abdominal aorta. Fats and connective tissues were removed from a section of the thoracic aorta, and 3-mm-wide aortic rings were prepared. For an endothelium-free aorta, the endothelial lining of each ring was removed by pressing the ring and rolling it gently onto a filter paper a few times. The endothelium was considered to be intact when relaxation induced by 1 μM of acetylcholine was over 20% of the maximal tension obtained by 60 mM KCl-induced contraction, and the removal of the endothelium was confirmed by the absence of acetylcholine-induced relaxation.

Vasodilative Effect of Cinnamaldehyde on Isolated Aortic Rings The aortic rings were mounted on steel hooks in a Magnus chamber (Kishimoto UC-5TD, Kyoto, Japan). One end of the aorta was attached to a force-displacement transducer (Kishimoto UM-203) so that its isometric contraction could be recorded (NEC RECTI-HORIZ-8K, Tokyo, Japan). The baths were filled with 5 ml of Krebs solution containing the following (mM): NaCl 120, KCl 4.7, $NaHCO_3$ 25.0, KH_2PO_4 1.2, $MgSO_4 \cdot 7H_2O$ 1.2, $CaCl_2$ 2.5, and glucose 10.0. The solution was maintained at 37 °C and bubbled continuously with 5% CO_2 in O_2 at pH 7.4. The rings were equilibrated for 45 min at an initial resting tension of 1 g. During this period, the Krebs solution in the bath was

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replaced every 15 min. 60 mM of KCl was added to the bath to contract the aortic strips. After the contraction reached a plateau, 1 μM of acetylcholine chloride was added. When the endothelium was removed, the acetylcholine chloride-induced relaxation disappeared. Then the Krebs solution was again replaced every 15 min for 60 min.

Each aortic strip with endothelium was contracted by treatment with $PGF_{2\alpha}$ (5 μM), NE (0.1 μM) or KCl (60 mM). When the contraction reached a plateau, cinnamaldehyde was added to the bath in cumulatively increasing doses of 1 μM—1 mM. Relaxation was expressed as percentage of the decrease in maximal tension obtained by $PGF_{2\alpha}$, NE or KCl-induced contraction.

To study endothelium-dependent relaxation, aortic strips with and without endothelium were contracted by treatment with $PGF_{2\alpha}$. When the contraction reached a plateau, cinnamaldehyde (1 μM—1 mM) and SNP (1 nM—0.1 mM) were added to the bath cumulatively. Furthermore, to study endothelium-dependent relaxation with nitric oxide/cGMP, aortic strips with endothelium treated by L-NAME (0.1 mM) and methylene blue (10 μM) for 60 min were contracted by treatment with $PGF_{2\alpha}$. When the contraction reached a plateau, cinnamaldehyde and SNP were added to the bath by the same schedule as mentioned above.

To study the relaxation caused by cinnamaldehyde, except NO-dependent relaxation, aortic strips with endothelium treated by L-NAME were used. They were pretreated with various inhibitors (10 μM propranolol, 0.1 mM theophylline, 1 mM TEA, 10 μM glibenclamide and 10 μM indometacin) for 15 min and contracted by treatment with $PGF_{2\alpha}$. When the contraction reached a plateau, cinnamaldehyde (1 μM—1 mM) was added to the bath cumulatively. Each inhibitor alone at the concentrations used had no effect on vasoconstriction.

Contraction Experiments The effect of cinnamaldehyde on contractions induced by the cumulative addition of calcium was studied. Ca^{2+}-induced contractions were elicited by the cumulative addition of $CaCl_2$ (1 μM—3 mM) to Ca^{2+}-depleted 60 mM K^+-containing Krebs solution for 10 min after the aorta strip had been suspended in Ca^{2+}-depleted Krebs solution. $CaCl_2$ was added directly to the bath fluid. Afterwards, using the same aortic rings, this procedure was repeated 10 min after the addition to the bath of 0.1 mM or 1 mM of cinnamaldehyde, or 1 μM of verapamil. Changes in contractile tension were expressed as percentage of the maximum tension obtained in the control curve.

Statistical Analysis Differences between specific means were tested by two-way repeated-measures ANOVA with *post hoc* analysis using the Bonferroni *t* test. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

Figure 1 shows that cinnamaldehyde caused dose-dependent vasorelaxation in $PGF_{2\alpha}$-, NE- and KCl-induced contraction, reaching a maximum of 90.0±2.4%, 60.6±8.2%, 36.5±8.8% at 1 mM of cinnamaldehyde, respectively (mean±S.E., $n=7$). Cinnamaldehyde caused dose-dependent vasorelaxation of the aorta with endothelium, without endothelium, and with endothelium treated by L-NAME in $PGF_{2\alpha}$-induced contraction. But the aorta with endothelium

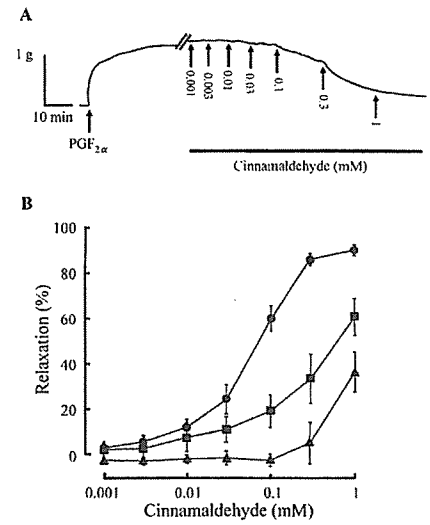

Fig. 1. Typical Recording (A) and Dose-Dependent Vasodilative Effect (B) of Cinnamaldehyde on Rat Aorta Strips

The aorta was contracted by 5 μM $PGF_{2\alpha}$ (●), 0.1 μM NE (■) or 60 mM KCl (▲), and the vasodilative effect of decrease was examined. Values are indicated as percentage of decrease in maximal tension by each of the vasoconstrictors. Vertical bars indicate S.E. ($n=7$).

dilated significantly compared to those without endothelium and with endothelium treated by L-NAME, reaching a maximum of 42.0±4.7%, 18.8±6.3%, and 22.2±3.1% at 0.1 mM of cinnamaldehyde, respectively (Fig. 2A, mean±S.E., $n=5$—7). SNP also caused vasorelaxation of the aorta with endothelium, without endothelium, and with endothelium treated by L-NAME in $PGF_{2\alpha}$-induced contraction. There were no statistically significant differences among the three groups (Fig. 2B). Furthermore, concerning aorta pretreatment with methylene blue (10 μM), vasorelaxation by cinnamaldehyde and SNP was decreased significantly compared to the aorta with endothelium not pretreated with methylene blue (Fig. 2).

The vasorelaxant effect of cinamaldehyde was examined with various compounds reported as inhibitors of vasodilatation. Vasorelaxation was not affected by propranolol, TEA, glibenclamide and indometacin (Fig. 3, $n=6$—8). There were no statistically significant inhibitory effects between the control group pretreated only with L-NAME and groups treated with various compounds reported as inhibitors of vasodilatation. But in the aorta treated with theophylline, the vasorelaxant effect of cinnamaldehyde was increased significantly compared to the control group pretreated only with L-NAME (Fig. 3, $n=8$, $p<0.01$ *vs.* control).

To evaluate the effect of the possible calcium antagonism of cinnamaldehyde, a series of experiments was performed, based on contracting the rat aortic preparations with increasing calcium concentrations in the presence and absence of different cinnamaldehyde concentrations. As shown in Fig. 4, the calcium response curve was significantly shifted to the right by 0.1 and 1 mM of cinnamaldehyde and by 1 μM of verapamil ($n=6$—7).

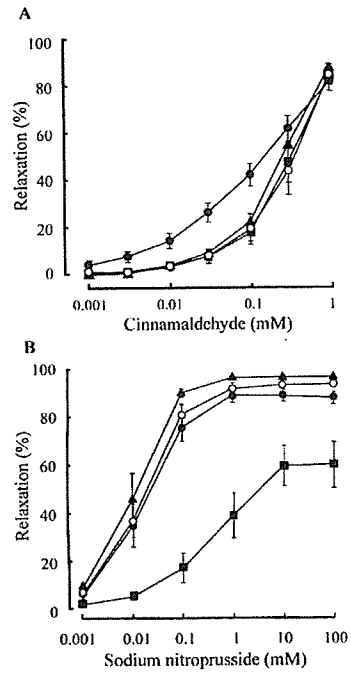

Fig. 2. Vasodilative Effects of Cinnamaldehyde (A) and SNP (B) on Endothelium-Denuded (○), Endothelium-Intact Aorta (●), Presence of 0.1 mM L-NAME (▲) and 10 μM Methylene Blue (■)

The aorta was contracted by 5 μM $PGF_{2\alpha}$, and the vasodilative effects of cinnamaldehyde and SNP were examined. Values are indicated as percentage of decrease in maximal tension by each of the vasoconstrictors. Vertical bars indicate S.E. Differences between endothelium-intact and endothelium-denuded were statistically significant (A, $p<0.05$; $n=5$—7). Differences between endothelium-intact and rings treated with methylene blue were statistically significant by two-way repeated-measures ANOVA (A, $p<0.05$; B, $p<0.01$; $n=7$).

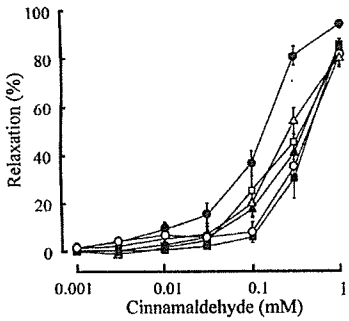

Fig. 3. Influence of Various Inhibitors on the Vasodilative Effect of Cinnamaldehyde

The aorta was treated with L-NAME and various inhibitors: 0.1 mM theophylline (●), 0.01 mM indometacin (△), 0.01 mM propranolol (□), 1 mM tetraethyl ammonium chloride (TEA, ■), 0.01 mM glibenclamide (○). The aorta was contracted by 5 μM $PGF_{2\alpha}$. Values are indicated as percentage of decrease in maximal tension by each of the vasoconstrictors. Vertical bars indicate S.E. Differences between rings treated with only L-NAME (control: ▲) and theophylline were statistically significant by two-way repeated-measures ANOVA ($p<0.01$, $n=6$—8).

DISCUSSION

Cinnamaldehyde is the main component of Cinnamomi Cortex. Cinnamomi Cortex is a crude drug used therapeutically in Asia and Europe. Even now it is used for a variety of diseases such as infectious disease, arthritis, cardiovascular

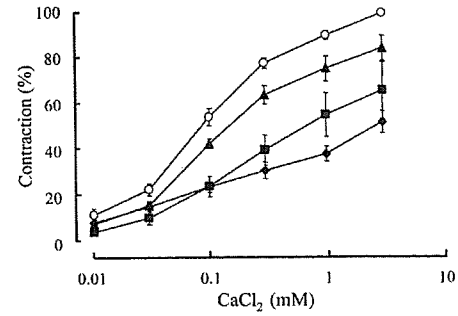

Fig. 4. Calcium Concentration–Contraction Curves of Isolated Rat Aorta in the Absence (○) and Presence of 0.1 mM (▲), 1.0 mM Cinnamaldehyde (■) and 1 μM Verapamil (◆)

The aorta was contracted by 60 mM KCl. The differences between control and rings treated with 0.1 mM cinnamaldehyde, 1.0 mM cinnamaldehyde, and verapamil were statistically significant by two-way repeated-measures ANOVA ($p<0.05$, $n=6$—7).

diseases, and so on. Cinnamomi Cortex contains 1—3% oil, and the main component of this oil is cinnamaldehyde, which constitutes about 90% of the oil.[8] As for other components of Cinnamomi Cortex, there are terpenoids and tannins, *etc.* The main active component is cinnamaldehyde, and it is thought to play a crucial role in the effect of Cinnamomi Cortex.

Mechanisms of the formulae containing Cinnamomi Cortex have been reported in regards to circulatory disease. Keishibukuryogan is reported to improve the microcirculation of the bulbar conjunctiva,[9] to protect vasofunction in a model of diabetic rat,[10] to decrease atherosclerosis in a model of hypercholesterolemic rabbit,[11] and so on. Concerning the mechanisms of these vasoprotective effects, keishibukuryogan is reported to exert an improvement effect on hemorheological factors[9,12] as well as an anti-oxidant effect.[13] As part of this formula, Cinnamomi Cortex is thought to have various effects on anti-platelet aggregation,[5,6] inhibition of thromboxane A2,[14] to have a vasorelaxation effect,[7] and so on.

As mentioned above, there are many reports concerning the effects of Cinnamomi Cortex on blood circulation, but there is no report about the effect of cinnamaldehyde on vasomotion. In this study, we demonstrated that cinnamaldehyde exerted both endothelium-dependent and -independent relaxant effects. As for endothelium-dependent relaxation, nitric oxide (NO) has been reported as an endothelium-derived relaxing factor (EDRF).[15,16] The vasorelaxant effects of cinnamaldehyde without endothelium and with endothelium treated with L-NAME became weaker than that with endothelium. In a word, the endothelium-dependent relaxing effects of cinnamaldehyde must result from EDRF/NO. Recently, in cultured cells, cinnamaldehyde was reported to stimulate endothelial NO synthase.[17] Now, we have also established that cinnamaldehyde had the same effect in an isolated vessel.

As EDRF/NO, NO is reported to lead the vasorelaxation through cGMP.[18] In this study, the cinnamaldehyde-induced relaxation with endothelium treated by methylene blue, which inhibits guanylate cyclase, decreased compared to control. It is reported that cGMP inhibits the adherence of leukocytes[19] and the activation of platelets.[20] Also, the concentration of cGMP in whole blood is related to the degree of

arteriosclerosis.[21] Based on these reports, it is suggested that the vasorelaxant effect by cGMP has vasoprotective effects.

Because cinnamaldehyde had a vasorelaxant effect without endothelium, it was clear that cinnamaldehyde had an endothelium-independent relaxant effect as well. To study this mechanism, we evaluated the effect of various inhibitors on cinnamaldehyde-induced relaxation, and found that none of them decreased the vasorelaxant effect of cinnnamaldehyde.

Because the vasocontractive effect by the administration of calcium was inhibited by cinnamaldehyde, as one of the mechanisms in the endothelium-independent relaxant effect, it was thought that cinnamaldehyde had an inhibitory effect on calcium influx to smooth muscle cells. The inhibitory effect of calcium influx not only has an antihypertensive effect but also an anti-arteriosclerotic effect.[22,23]

But there was also a report that cinnamaldehyde had a vasorelaxant effect similar to that of papaverine.[24] In addition, the relaxation effect by cinnamaldehyde was most remarkable in $PGF_{2\alpha}$-induced contraction in this study, strongly suggesting that cinnamaldehyde affects the function of the $PGF_{2\alpha}$-receptor.

Recently, in terms of crude drug components, galloylglucose[25] and arecoline,[26] *etc.*, have been reported to possess an endothelium-dependent vasodilatative effect, and perillaldehyde[27] and olleuropeoside,[28] *etc.*, to have an endothelium-independent effect. However, a component of crude drugs having both effects has as yet not been reported. The endothelium-dependent and -independent relaxant effects of cinnamaldehyde that were revealed in the present study possibly have different actions against vascular injury. These effects are thought to play important roles in formulae containing Cinnamomi Cortex.

In this study, the relaxation induced by cinnamaldehyde treated with L-NAME increased under the condition of pretreatment with theophylline, a phosphodiesterase inhibitor reported to have antagonistic effects on adenosine receptor and inhibitory effects on intracellular Ca^{2+} release.[29] We used high-dose theophylline treatment preceding the administration of cinnamaldehyde to vessels. As the concentration of cAMP was thought to increase sufficiently in smooth muscle, cinnamaldehyde could not increase the cAMP concentration any further. So it is thought that there is positive interaction between theophylline and cinnamaldehyde in terms of the vasorelaxant effect, rather than participation in the phosphodiesterase inhibitory effect.

As mentioned above, cinnamaldehyde induces both endothelium-dependent and -independent relaxation, and these effects are thought to be related to the vasoprotective effect of formulae containing Cinnamomi Cortex. To continue with this line of reasoning, *in vivo* studies of the effects of cinnamaldehyde on the circulatory system are now called for.

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ORIGINAL COMMUNICATION

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Differentiating Alzheimer's disease from subcortical vascular dementia with the FAB test

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Abstract *Background* The frontal assessment battery (FAB) test is a composite tool for assessing executive functions related to the frontal lobe. Neuropsychological and blood-flow studies indicate distinct patterns of deterioration of anterior and posterior cortical function in Alzheimer's disease (AD) and subcortical vascular dementia (VD) patients. We predict that the FAB score may be useful for discriminating VD from AD. *Objective* To evaluate the clinical usefulness of the FAB test for differential diagnosis of AD and VD. *Methods* We compared FAB scores in 25 patients with AD, 27 patients with VD, and 80 age-matched normal control subjects. The AD group was matched for age, education and MMSE score with the VD group. The subtest scores in FAB were also compared among the three groups. *Results* The FAB scores were significantly decreased in both the AD and VD groups compared to the control group, and the reduction were greater in the VD group. Among the FAB subtests, mental flexibility (phonological verbal fluency) was the only subtest that significantly discriminated VD from the other two groups. *Conclusions* The FAB test can provide useful information for differentiating AD and VD at the bedside.

Key words frontal lobe function · verbal fluency · cognitive impairment · discrimination analysis · executive function

Introduction

Development of a short standardized mental status examination is helpful for bedside assessment of cognitive functions and for diagnosis of neurological disorders. The established neuropsychological tests of frontal lobe functions such as the Wisconsin Card Sorting Test (WCST) [12] and Stroop Test [13] are relatively time-consuming, and are both difficult and distressing for brain-damaged patients. The original study reported that the frontal assessment battery (FAB) score was highly correlated with the WCST score, while it was unrelated to the Mini-Mental State Examination (MMSE) score [4]. Thus, cognitive impairments overlooked in MMSE could be detected with FAB. The study also showed that ninety percent of patients with frontal lobe dysfunction could be discriminated from normal controls. The FAB test has been validated for differential diagnosis of fronto-temporal dementia (FTD) and Alzheimer's disease (AD) with high sensitivity and specificity [16].

The FAB test has recently been applied to several clinical populations [10, 14]. Rodriguez et al. reported that it provides a reliable measure of fronto-subcortical deterioration in several neurological

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disorders [14]. However, no report has directly compared the FAB score in patients with AD and vascular dementia (VD), although AD and VD are the two commonest cause of dementia in aged people. Many studies have reported differences in cognitive impairment profiles between AD and VD [6, 7, 8, 18]. The general consensus is that episodic memory is more impaired in AD, whereas executive/attentional processing is more impaired in VD. The usual basic neuropsychological battery test for frontal lobe function is the WCST. Since the previous study demonstrated a good correlation between the WCST and FAB scores [4], the FAB might be a useful means for assessing impaired frontal executive functions in VD in comparison with AD. We compared the FAB scores in patients with AD and VD to test the hypothesis that the FAB score could reliably discriminate VD from AD.

Methods

We studied two patient groups, which consisted of 25 patients with AD (aged 73.1 ± 7.6 years, (mean ± SD)), and 27 patients with VD associated with subcortical stroke (74.9 ± 6.2 years.). Diagnostic criteria were as follows. The diagnosis of AD was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [9]. All AD patients showed progressive cognitive deterioration and episodic memory impairment, and were diagnosed probable AD. The diagnosis of VD was made according to criteria proposed by the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke at an International Workshop with support from the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) [15]. All VD patients had been diagnosed probable VD with ischemic stroke in subcortical regions. We excluded patients with cortical stroke lesions, because they sometimes showed aphasia or apraxia, which might affect the evaluation with the FAB. The VD patients had mild motor impairments as measured by a low mean National Institute of Health Stroke Scale (NIHSS) of 3.8. Sites of subcortical infarct were white matter in 13 patients (40.7%), striatocapsular region in 11 patients (48.1%), multiple sites in 2 patients (7.4%), and thalamus in one patient (3.7%). As a normal control (NC) group, we studied 80 neurologically normal subjects. No subjects had a history of psychiatric disorder or substance abuse. A summary of the demographic data is given in the Table 1. The AD group was matched for age, education and MMSE score with the VD group, and both dementia groups were also matched for age and education with the NC group.

Magnetic resonance imaging (MRI) was employed to explore organic brain changes in all patients. The imaging study was carried out on a 1.5 Tesla unit (GE Medical Systems or Signa Horizon Cvi). Hippocampal and medial temporal lobe atrophy in AD, and multiple or single subcortical stroke lesions in VD were confirmed by MRI examination. Three out of 27 VD patients showed mild atrophy in hippocampus and medial temporal lobe, but we classified them into the VD group based on their clinical course and ischemic lesions on MRI. The NC subjects also received MRI examination in addition to complete neurological and neuropsychological assessments. No subjects in the NC group showed any ischemic lesion or abnormal atrophy on MRI.

All subjects underwent the FAB test and MMSE. The FAB test consists of six subtests, including item 1; similarities (conceptualization), item 2; verbal fluency (mental flexibility), item 3; motor series (motor programming), item 4; conflicting instructions (sensitivity to interference), item 5; Go/No go (inhibitory control) and item 6; prehension behavior (environmental autonomy). Each subtest score ranges from 0 (worst) to 3 (best). The total FAB score was calculated by adding the scores in the six subtests, and ranges from 0 (worst) to 18 (best). Both the total and subtest scores were used for evaluation. Examiners for the FAB were blind to clinical diagnosis and neuroimaging findings. We excluded demented subjects dosed with a cholinesterase inhibitor to minimize efficacy of cognitive enhancers improving executive functions [3].

Statistical evaluation was performed with non-parametric tests for the total FAB score and subtest scores, because the scores did not show normal distributions. The Kruskal-Wallis test was used for three-group comparison (NC, AD, VD) and four-VD subgroup comparison (white matter, striatocapsular region, multiple sites, thalamus). The post-hoc analysis was performed with the Mann-Whitney U test. A level of $p < 0.05$ was accepted as statistically significant.

Table 1 Demographic and neuropsychological data for study groups

Variables	NC (n = 80)	AD (n = 25)	VD (n = 27)	p value	Post hoc comparisons
Age (years)	73.5 ± 5.0	73.1 ± 7.6	74.9 ± 6.2	NS	–
Education (yr)	9.1 ± 2.5	9.0 ± 2.1	9.9 ± 1.7	NS	–
Duration (yr)	–	2.9 ± 1.8	2.1 ± 4.0	< 0.01	AD > VD
MMSE	28.9 ± 1.2	21.6 ± 3.6	21.4 ± 4.1	< 0.0001	NC > AD = VD
Total FAB	15.1 ± 1.7	13.2 ± 1.9	10.7 ± 2.7	< 0.0001	NC > AD > VD
Item 1	2.0 ± 0.8	2.0 ± 0.5	1.7 ± 0.8	NS	–
Item 2	1.9 ± 0.9	1.7 ± 0.9	0.5 ± 0.8	< 0.0001	NC = AD > VD
Item 3	3.0 ± 0.2	2.7 ± 0.6	2.4 ± 0.8	< 0.0001	NC > AD = VD
Item 4	2.8 ± 0.4	2.2 ± 0.8	1.8 ± 1.0	< 0.0001	NC > AD = VD
Item 5	2.4 ± 0.7	1.3 ± 0.6	1.3 ± 1.0	< 0.0001	NC > AD = VD
Item 6	3.0 ± 0.1	3.0 ± 0.0	2.8 ± 0.6	< 0.05	NC > VD, NC = AD AD = VD

Values are presented as mean ± SD
Item 1; conceptualization, Item 2; mental flexibility, Item 3; motor programming, Item 4; sensitivity to interference, Item 5; inhibitory control, Item 6; environmental autonomy
NC = normal controls, AD = Alzheimer's disease patients, VD = vascular dementia patients, MMSE = Mini-Mental State Examination

Results

All results are shown in the Table 1. The MMSE scores in both patient groups were significantly lower than that in the NC group, but no significant difference in the MMSE score was found between the AD and VD groups. The Kruskal-Wallis test showed significant differences in the total FAB score among the three groups. The post-hoc Mann-Whitney test revealed that the total FAB score was significantly lower in the AD group than in the NC group ($U = 440.5$, $p < 0.0001$). The score in the VD group was significantly lower than those in both the NC ($U = 219.0$, $p < 0.0001$) and AD groups ($U = 150.5$, $p < 0.001$).

The analysis of the subtest demonstrated that the scores in the item 2 (mental flexibility), 3 (motor programming), 4 (sensitivity to interference) and 5 (inhibitory control) subtests showed highly significant inter-group differences, and small but significant differences were also observed in the item 6 (environmental autonomy) subtest scores among the three groups. The item 1 (conceptualization) score showed no difference among the three groups. The post-hoc analysis for the subtest score in item 2 (mental flexibility) showed that the VD group had a lower score than those in the NC ($U = 303.0$, $p < 0.0001$) and AD groups ($U = 105.5$, $p < 0.0001$), but there was no significant difference between the AD and NC groups. The scores in item 3 (motor programming), item 4 (sensitivity to interference) and 5 (inhibitory control) showed same patterns; the VD and AD groups had lower scores than the NC group ($U = 676.0$ and $U = 834.5$, $p < 0.0001$ and $p < 0.01$ for item 3, $U = 390.5$ and $U = 465.5$, $p < 0.0001$ for item 4; $U = 568.5$ and $U = 306.5$, $p < 0.0001$ for item 5). The differences between the AD and VD groups were not significant. The score in item 6 (environmental autonomy) was significantly lower only in the VD group compared with the NC group ($U = 972.5$, $p < 0.05$).

We did not find any effects of lesion site on the FAB score in the VD group; there were statistically no differences in the total FAB and six subtest scores among the VD patients who had ischemic lesions in white matter, striatocapsular region, thalamus or multiple sites.

Discriminant validity

The total FAB score was applied to the discriminant analysis between VD and AD. It could correctly classify 85.7% of VD and 71.0% of AD, when the cutoff score was 11 ($F = 13.248$, Wilks' lambda = 0.791, $p < 0.01$). The patient is diagnosed as having VD when the total FAB score is less than or equal to 11, whereas the patient is classified as AD when the score is greater than 11. Item 2 (mental flexibility) was also applied for the discriminant analysis between VD and AD. The score of item 2 classified 94.4% of VD and 70.6% of AD, when the cutoff score was 0 ($F = 28.971$, Wilks' lambda = 0.633, $p < 0.001$). The patient is diagnosed as having VD when the result is equal to 0, whereas the patient is classified as AD when the result is greater than 0. Forward stepwise discriminant analysis with the total FAB and item 2 could correctly classify VD by 100% and AD by 80.8% ($F = 23.573$, Wilks' lambda = 0.618, $p < 0.001$).

Discussion

Our results showed that there was a greater reduction in the total FAB scores in VD than in AD, and we could distinguish VD from AD reliably by using the combination of the total FAB score and the subtest score for item 2 (mental flexibility). This is consistent with the previous report that frontal executive functions are more impaired in VD than in AD [6]. Mok et al. reported that the total FAB was 8.9 points in subcortical VD, which was lower than our data probably due to advanced clinical stage with higher mean NIHSS scores (= 4.7) than our study (= 3.8) [10]. A prominent disturbance of frontal lobe function in VD has been demonstrated with a wide range of assessment tools for brain functions, including neuropsychological tests, single photon emission tomography, positron emission tomography, and electroencephalography [7, 11, 17, 20, 21]. The relative preservation of the FAB score in AD patients is also consistent with the report that the FAB scores are higher in patients with AD than in those with FTD [16]. However, when the FAB score in AD was compared with that in the control group, there was a significant reduction in AD. Graham et al. employed several neuropsychological test batteries for executive function in AD in addition to VD and age-matched controls [6]. In their study the WCST and Stroop test scores showed similar reductions in AD and VD versus the controls. This suggests that some frontal executive functions may be compromised in AD, and the analysis of the FAB subtest scores might be useful for clarifying this point.

Among the FAB subtests, item 2 (mental flexibility) was significantly impaired in the VD group compared with the AD group in the present study. In the item 2 (mental flexibility) subtest, subjects are required to produce as many words beginning with a given Japanese consonant as they can in a limited period of time. This task places heavy demands on the central executive function with the initiation of effective

retrieval strategies to organize thinking and the flexibility of search and retrieval processes. In general, there are two types of word fluency tasks; phonemic and semantic fluency. The current study employed the paradigm for phonemic fluency, which has been thought to be a test of frontal lobe function, including the middle frontal gyrus, inferior frontal gyrus, and supracallosal medial frontal cortex [2, 5]. The blood flow studies have demonstrated that the activations were observed not only in the left hemisphere, but also in the right hemisphere [1]. Such a widely distributed network for phonemic verbal fluency could be easily impaired by subcortical ischemic damage.

Relative preservation of verbal fluency in AD is consistent with the other neuropsychological reports [6]. In the evolution of AD pathology, neurofibrillary tangles appear to spread to the infero-lateral temporal, inferior parietal, posterior cingulate and ventral frontal regions, following involvement of the medial temporal structures. Involvement of the dorsolateral prefrontal cortex and medial frontal cortex appears to occur much later. This might account for the relative sparing of subtest scores in mental flexibility (phonemic verbal fluency) in AD compared to VD. The score of subtest item 2 in the control group was comparable to the AD group. This result is in agreement with a previous report that similar to AD healthy older subjects had performed significantly worse on semantic category fluency than younger subjects [19].

The discrimination power of the FAB test appears to be relatively high enough to differentiate AD and VD in the mild to moderate stage of dementia. When the cutoff score of 11 for the total FAB score and that of 0 for item 2 (mental flexibility) subtest were applied, all AD subjects were correctly diagnosed, although some VD patients were wrongly classified as AD. Intriguingly, the cut-off score for the best discrimination of AD and FTD was reported to be 12 points [16], which is similar to the value for discriminating AD and VD in the present study. The present study indicates that the FAB could be a useful clinical tool at the bedside in differential diagnosis of AD and VD albeit of limited sensitivity and specificity in the individual case as there was some overlap of the FAB scores between AD and VD groups.

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アパシー（意欲低下）と認知機能

小林　祥泰

Key words: apathy, depression, stroke, vascular dementia, prefrontal function, disuse syndrome

【要旨】 Luriaの脳機能の3つの単位系で戦略など最高次機能を司るのが前頭前野である。血管性痴呆（VD）ではアルツハイマー型老年期痴呆（SDAT）に比してこの機能低下が目立つのが特徴である。VDではうつ状態が多いと云われるが実際にはアパシーの合併頻度が高い。アパシーとうつ状態は明らかに異なるものである。血管性うつ状態の定義からもそのことが示唆される。筆者らのやる気スコアはアパシーの評価に有用である。脳梗塞でアパシーを呈する群では前頭前野脳血流が有意に低い。また、尾状核周辺の病変がアパシーに関与している。脳卒中では初回から痴呆になることは稀であり、アパシーが廃用症候群を介してVDを促進していると考えるのが妥当である。

はじめに

Luria[1]は脳機能の3つの単位系すなわち、脳幹網様体賦活系（覚醒）、大脳新皮質（認知、記憶）、前頭前野（遂行機能）をあげており、前頭前野が最高次機能を司っている。遂行機能の中で最も大事なものはやる気である。どんなに優れたworking memoryを持っていても動機付けがないと人は優れた仕事をすることが出来ない。痴呆になればアパシー（自発性低下、無気力）は二次的に必然的に起こるものだとする考え方もある。しかし、実際の臨床ではVDでアパシーが多いことが知られている。これはVDの大半は皮質下性痴呆であり、皮質下性痴呆は背外側前頭前野回路を中心とする基底核、視床などの諸核やその投射路である白質が障害されて起こる前頭葉性痴呆であることによる[1]。近年、脳卒中後うつ状態が注目されてきたが、そのうちの多くはアパシーの要素がむしろ強いことも明らかにされつつある。

I. アパシーと抑うつの頻度

Mirakhurら[2]はアルツハイマー型痴呆435例のBPSD（周辺症状）を12項目に分類して統計解析し、4つの因子に分類出来たとしている。第1因子は感情障害因子で抑うつや焦燥、不安、興奮など、第2因子は身体行動的因子でアパシー、異常言動、睡眠障害、摂食障害など、第3因子は精神医学的因子で、幻覚、妄想など、第4因子が軽躁状態因子で脱抑制や多幸が含まれるとしている。全経過中頻度なので通常の断面調査による頻度よりも高くなっているが、アパシーが76%と最も高率で、抑うつは54.3%で6番目である。

アパシーは一見すると抑うつと似ているので混同されやすいが、抑うつは感情障害因子、アパシーは身体行動因子に分類される異なった症状であることに注意を要する。基本的に皮質下性痴呆であるVDにおいてはアパシーの関与はさらに大きく、Cummings[3]はほぼ普遍的に出現する症状と位置づけている。Newman[4]は痴呆の発症率を調査する18大学共同の疫学調査Canadian Study of Health and Agingの中から抑うつについての調査を行った2,344名のデータを用いて解析している。その中には481名のアルツハイマー型痴呆、140名のVDがみられ、各々の大うつ病の頻度は前者で3.2%、後者で21.2%と後者で有意に高く、年齢や痴呆の重症度、抗うつ薬などを調整したオッズ比もVDで8.2と高値であったことから、VDで明らかに抑うつが強いことを確認したとしている。筆者らのZungの自己記入式抑うつ度調査票による抑うつ度（SDS）とやる気スコア（apathy scale）[5]による検討では抑うつはVDで約2倍の頻度にみられ、アパシーも約1.5倍と明らかに高率であった。また、筆者らがVDも含む外来通院可能な脳梗塞245例で調査した結果では、抑うつ単独は12%でアパシーとの合併が24%、アパシー単独が21%と抑うつよりもアパシーの頻度が明らかに高く、いわゆる脳卒中後抑うつと云われているもののかなりの頻度はアパシーの要素が強いものであることを示唆している[6]。

Brodatyら[7]はSydney Stroke Studyで135例の脳梗塞（発症3-6ヵ月後）と92名の対照群でApathy Evaluation

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Scaleを評価した結果、アパシーが26.7%と対照群の5.4%に比し有意に多かったとしている。自己記入式の抑うつ度調査では弱い相関がみられたが、臨床診断では相関はみられなかった。また、アパシー群ではMMSEが有意に低く、年齢と発病前知能、抑うつ度スコアで補正した後でも注意力低下と情報処理速度の低下が認められたとしている。

II. アパシー、抑うつと前頭前野

PETによる研究によると、抑うつでは特に精神運動抑制が強い例で前頭前野と前部帯状回でブドウ糖代謝低下が著明であるとされている。Robinsonら[8]は脳卒中後うつ病は病変が左前頭極に近いほど起こりやすいことを指摘し、脳卒中後うつ病は器質的うつ病であるとした。その後彼等はPETでセロトニン代謝の低下も左前頭葉で生じていることを明らかにした[3]。早期アルツハイマー型痴呆（平均MMSE 22.5）でアパシーと抑うつのある群とない群をPETで比較した研究ではブドウ糖代謝が前者では左眼窩前頭皮質で低下していたのに比し、後者では背外側前頭前野で低下しており、両者の発現する脳内回路が異なっていることを推測している[9]。筆者らのXe133吸入法を用いた局所脳血流測定による検討でも脳卒中患者におけるアパシー群では図1のように前頭前野を中心に脳血流の低下が認められた[10]。したがって、アパシーも抑うつも前頭前野と密接な関係を有することが明らかである。

前述したBrodaty[7]らはMRIによる評価で、右半球病変例にアパシーが多く特に前頭葉皮質下回路病変が関与していたと報告している。

この事実は前頭葉性痴呆を呈する脳卒中でアルツハイマー型痴呆よりもアパシーや抑うつが出現しやすいことと一致している。

III. アパシーと認知機能

Zawackiら[11]はVDのADL自立に対してアパシーが独立した重要な因子であることを強調している。すなわち、ADLスコア全体ではアパシーの関与が36%におよび、痴呆の重症度の関与は15%であった。基本的ADLスコアに対してはアパシーの関与が27%と最も大きく、痴呆重症度や実行機能などは有意な関与を認めなかった。道具使用ADLスコアでは痴呆の重症度が最も大きく37%を占めたがアパシーも14%と有意の関与を示した。以上より、VDでは日常生活自立に全般的認知機能よりもアパシーがより密接に関与していることが明らかになったとしている。筆者らはアパシーをみる簡便な指標として「やる気スコア」（表1）[5]を用いているが、これが健常高齢者においても前頭葉機能も含まれるKohs' block design testなどの認知機能と相関し、特にVDの早期発見に役立つ可能性を見いだした。SDSと年齢を加えて多変量解析を行った結果でもアパシーのみが有意な相関を示した。したがってアパシーはVDにおける実行機能低下と密接に関連している可能性が強い。

Levyら[12]はSDATやパーキンソン病、進行性核上性麻痺、前頭側頭型痴呆などの症例で標準的なNeuropsychiatric Inventoryを用いて抑うつとアパシーを評価し、認知機能との関係を検討している。その結果アパシーと抑うつは相関せず、また、MMSEでみた認知機能もアパシーのみで有意な相関を認めたと報告している。

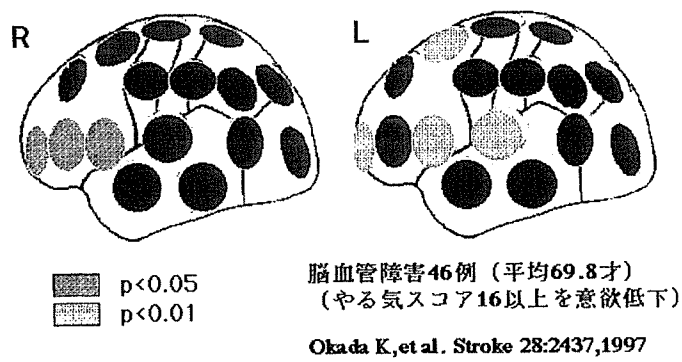

図1. 脳血管障害におけるやる気低下（アパシー）群の局所脳血流低下部位

表 1. やる気スコア（apathy scale 島根大学版）

やる気スコア	全くない	少し	かなり	大いに
1) 新しいことを学びたいと思いますか？	3	2	1	0
2) 何か興味を持っていることがありますか？	3	2	1	0
3) 健康状態に関心がありますか？	3	2	1	0
4) 物事に打ち込めますか？	3	2	1	0
5) いつも何かしたいと思っていますか？	3	2	1	0
6) 将来のことについての計画や目標を持っていますか？	3	2	1	0
7) 何かをやろうとする意欲はありますか？	3	2	1	0
8) 毎日張り切って過ごしていますか？	3	2	1	0
	全く違う	**少し**	**かなり**	**まさに**
9) 毎日何をしたらいいか誰かに言ってもらわなければなりませんか？	0	1	2	3
10) 何事も無関心ですか？	0	1	2	3
11) 関心を惹かれるものなど何もないですか？	0	1	2	3
12) 誰かに言われないと何にもしませんか？	0	1	2	3
13) 楽しくもなく、悲しくもなくその中間位の気持ちですか？	0	1	2	3
14) 自分自身にやる気がないと思いますか？	0	1	2	3
			合計	

（島根医科大学第 3 内科版：16 点以上をやる気低下と判定）
Starkstein SE, et al. (1993) Apathy following cerebrovascular lesions. Stroke 24, 1625-1630 から翻訳作成

IV. VD はアパシーによる廃用性痴呆

Framingham study の 12 年間の調査[13]では脳卒中発症者に発症 6ヵ月後の認知機能低下（MMSE 27 から 24）がみられたと報告されている。この群では抑うつも高率にみられたが、多変量解析では抑うつとは独立して脳卒中罹患が認知機能低下の危険因子であったとしている。認知機能低下の促進因子としては左半球の大病変が関与する傾向がみられたのみであった。一方、Bokura ら[14]は脳卒中で尾状核頭部を含む病変とそれ以外の皮質下病変例の MMSE の短期（3-6ヵ月）と長期（1-2 年）の変

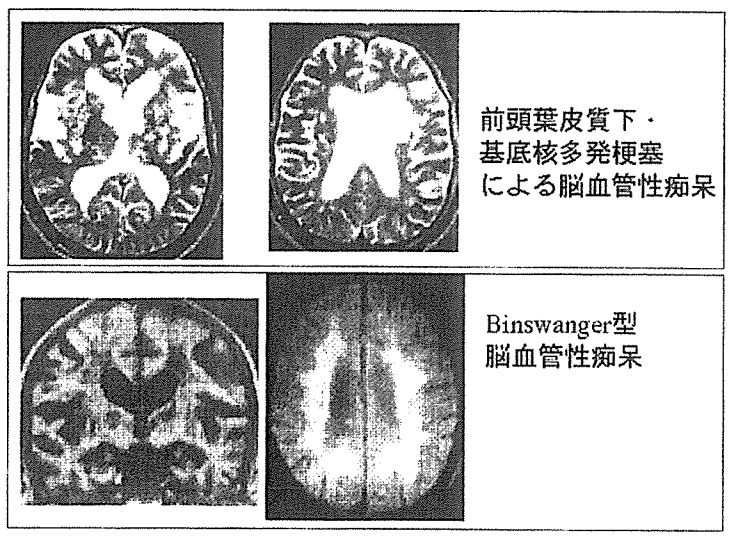

図 2. VD の典型例の MRI 所見
上段は前頭葉皮質下・基底核多発梗塞によるもの。下段は Binswanger 型 VD で広範なびまん性高信号域と多発性ラクナ梗塞、脳萎縮が認められる。

化を検討し、前者では有意差はなかったが、後者では左右とも尾状核頭部病変例でその他群に比して有意にMMSEが低下したことを報告している。この結果は尾状核頭部病変それ自体が認知機能低下の原因ではなく、認知機能低下の進行を促進する原因となった可能性を示唆している。前述したように筆者らのアパシーと局所脳血流量の関係の検討ではアパシーは前頭前野血流と有意な関連を示していた。すなわち、尾状核頭部病変は前頭前野への投射系障害をきたし、アパシーをきたした可能性が考えられる。その結果、長期的にみると認知機能低下が生じた、すなわち、これはアパシーによる廃用性認知機能低下である可能性が強いと考えられる。

VDは初回の脳卒中で起こることは少なく再発を繰り返すことが重要とされているが、単なる再発の回数ではなく、尾状核頭部周囲病変の有無が重要である。図2上段は多発ラクナ梗塞で痴呆になった例と下段はBinswanger型VDのMRI所見である。両者共明らかに尾状核萎縮が生じていることが分かる。上段の例は筆者が10年以上治療していたが、難治性高血圧があり再発を繰り返しアパシーが進行して次第に痴呆になった例である。したがって、典型的な多発性ラクナ梗塞によるVDあるいはBinswanger型VDではアパシーが先行し、白質病変によるネットワーク障害を基礎とした廃用性痴呆に進行すると考えた方が妥当と思われる。すなわち、アパシーはVDの初期症状であると同時に廃用性痴呆の原因として重要であると考えている。

おわりに

アパシーは多発性脳梗塞などの前頭前野への投射路障害で生じやすい。その結果として廃用性痴呆に進行する可能性が高く、アパシーはVDの症状の一つと云うより、その原因として重要であることを強調したい。

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