The effects of phosphatidylserine and omega-3 fatty acid-containing supplement on late life depression

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Abstract

Late life depression is often associated with a poor response to antidepressants; therefore an alternative strategy for therapy is required. Although several studies have reported that phosphatidylserine (PS) may be effective for late life depression and that omega-3 fatty acids DHA and EPA have also proven beneficial for many higher mental functions, including depression, no concrete conclusion has been reached. This study was performed to clarify the effect of PS and omega-3 fatty acid-containing supplement for late life depression by not only clinical evaluation but also salivary cortisol levels. Eighteen elderly subjects with major depression were selected for the study. In all, insufficient improvement had been obtained by antidepressant therapy for at least 6 months. The exclusion criteria from prior brain magnetic resonance images (MRI) included the presence of structural MRI findings compatible with stroke or other gross brain lesions or malformations, but not white matter hypersensitivities. They took a supplement containing PS 100 mg, DHA 119 mg and EPA 70 mg three times a day for 12 weeks. The effects of the supplement were assessed using the 17-item Hamilton depression scale (HAM-D17) and the basal levels and circadian rhythm of salivary cortisol. The study adopted them as indices because: salivary cortisol levels are high in patients with depression, their circadian rhythm related to salivary cortisol is often irregular, and these symptoms are alleviated as depression improves. The mean HAM-D17 in all subjects taking the supplement was significantly improved after 12 weeks of taking the supplement. These subjects were divided into 10 non-responders and 8 responders. The basal levels and circadian rhythm of salivary cortisol were normalized in the responders while not in non-responders. PS and omega-3 fatty acids, or other elements of the supplement, may be effective for late life depression, associated with the correction of basal levels and circadian rhythm of salivary cortisol.

Introduction

Phosphatidylserine (PS) is an acidic phospholipid that is a natural component of the brain neuronal membrane. PS is a minor percentage of the phospholipids that compose biological membranes, but may be especially important in determining neuronal membrane surface potential and the local ionic environment, and thus is indispensable for a normal neuronal activity.[1] Because of such potential importance in neuronal functioning, PS is informally characterized as a brain-specific nutrient.[2] As PS within the neural membrane is especially important for the activation of protein kinase C (PKC) and PKC activity declines with age,[3] it is speculated that there are age-related deficits in PS in humans. A decrease in PS in the brain with aging may relate to cognitive decline and impairment. Pharmacokinetics studies indicate that exogenous PS crosses the blood-brain barrier,[4] and the effects of PS on cognitive decline and impairment have been reported.[5-7] In these studies, PS extracted from the bovine cortex (BC-PS) was used. Because of the risk of bovine spongiform encephalopathy, however, BC-PS is not used and soybean-derived PS (Soy-PS) is used currently. Although it is controversial whether the effects of Soy-PS on cognitive function are identical to those of BC-PS,[8] a recent double-blind, placebo-controlled study revealed that 6 months of Soy-PS supplementation could improve the memory function of the elderly with memory complaints.[9] The benefits of PS are not restricted to middle-aged and elderly people. In young, healthy males, PS can improve the process of coping with stress and significantly counteract stress-induced activation of the hypothalamo-pituitary-adrenal (HPA) axis.[10,11] In children, PS improved attention deficit/hyperactivity disorder (ADHD).[12] This indicated that PS may be able to correct disrupted neuron function under various conditions. From clinical experience, the improvement of depressive symptoms was seen in a study of the effect of PS on cognitive impairment and therefore a study of the effect of PS on depression was planned. Previous reports have identified the effect of PS on late life depression in women.[13,14] These reports found effects of PS on depression, but did not find any biological change accompanied by the improvement of depressive symptoms. On the other hand, dietary supplementation with omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) has proven beneficial for many higher mental functions.[15] Previous studies indicate the effectiveness of DHA and EPA combinations on various disorders, including ADHD,[16] dementia,[17] and depression.[18,19] Omega-3 fatty acids function exclusively via cell membranes, in which they are anchored by phospholipid molecules. They have an obvious and predictable synergy with other cell membrane nutrients, specifically phospholipids including PS, and antioxidants including intrinsic oxidants and extrinsic oxidants.[15] Utilizing DHA and EPA together with phospholipids and membrane antioxidants to achieve a *triple cell membrane synergy* may further diversify their current wide range of clinical applications;[15] therefore, in the present study, the effect of PS alone was not seen but a supplement containing DHA and EPA in addition to PS was used.

Thus, the aim of the present study was to evaluate the effects of a PS and omega-3 fatty acid-containing supplement on late life depression. The subjects of the present study were the elderly who had not responded to common antidepressants. The study assessed not only the clinical effects of the supplement, but also its effects on the basal salivary cortisol level and circadian rhythm related to cortisol.

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Materials and Methods

Subjects

Subjects who fulfilled the 5 items described below and regularly visited the Psychiatry Department out-patient clinic of Mie University Hospital were selected: i) 65 years old or more, ii) insufficient improvement achieved [improvement of 25% or more was not seen on the 17-item Hamilton depression scale (HAM-D17)], despite treatment with the usual antidepressant therapy for at least 6 months, iii) present HAM-D17 corresponds to

major depression on DSM-IV by 18 points or more, iv) cognitive impairment has not been identified (Mini-Mental State Examination total score is higher than 24),[20] and v) an organic background, including structural MRI findings compatible with stroke or other gross brain lesions or malformations has not been identified except for atrophy of the brain corresponding to age. The presence of WMH was not included in the exclusion criteria. Eighteen normal healthy age- and sex-matched controls (10 men and 8 females, 69.6±2.8 years old) were selected to compare the basal levels and circadian rhythm of salivary cortisol. Moreover, 18 age- and sex-matched depressed subjects (10 men and 8 females, 67.9±3.5 years old), for whom antidepressants had succeeded were compared to those of subjects taking the supplement. The experimental protocol was approved by the Ethics Review Committee for Human Experimentation of Mie University Graduate School of Medicine and all subjects gave their informed consent.

Phosphatidylserine and omega-3 fatty acid-containing supplement administration

Treatment with antidepressants and other drugs was continued without any change, but one supplement package (Nutrix Kefarin™ plus; ab ovo Inc., Japan, which contains PS 100 mg, DHA 119 mg, EPA 70 mg, DPA 11 mg, γ-linolenic acid 50 mg, astaxanthine 2 mg, and Palm Tocotrienol Complex 16 mg) was taken three times a day. The effects of taking the supplement for 12 weeks were examined by HAM-D17 and cortisol levels in the saliva. Except for one man who disliked the taste of the supplement and dropped out, the study of 18 cases (10 men and 8 females, 68.5±3.2 years old) was completed.

Salivary cortisol measurement

The subjects attended the hospital every four weeks. On the consultation day, immediately after waking up, one hour, two hours and three hours after waking up, saliva samples were collected using cotton dental rolls (Salivette; Sarstedt, Nümbrecht, Germany) and immediately stored at –4°C. The subjects brought the saliva samples to the hospital frozen in a cooler. During the consultation, saliva samples were collected four hours after waking up. The cotton dental rolls were stored on ice until they were centrifuged for 5 min at 2400 rpm and 4°C. The saliva samples were then stored at –20°C until cortisol levels were determined. The cortisol levels in saliva were also measured immediately after waking up, one hour, two hours, three hours and four hours after waking up in the normal controls. Using a microplate reader (Sunrisremote, Wako, Japan) and amylase assay kit (Salimetrics, State College, PA, USA), the levels of cortisol were measured.

Statistics

The depressive state was evaluated by HAM-D17 at consultation every four weeks and compared by ANOVA with the value before supplement administration. The salivary cortisol level four hours after waking up was used as the basic value for comparative study and was compared with the level before supplement administration by t-test. The cortisol level was also compared with the normal controls by t-test. For the circadian rhythm of salivary cortisol four hours after waking up, the appearance time of the peak was examined. For the frequency of a peak value being seen immediately after waking up, the chi-square test was used between the PS group and control group.

Results

Hamilton depression scale

As shown in Figure 1A, HAM-D17 was 14.6±5.9 after taking the supplement for 12 weeks, which was significantly low compared to 21.1±3.4 at the start (P=0.02). The subjects were divided into 10 non-responders who maintained a change of 25% or less and 8 responders in whom HAM-D17 improved by 25% or more. Comparing responders with non-responders, there were significant differences 8 weeks and 12 weeks after supplement administration (P=0.1 and 0.04, respectively), while there was no significant difference 4 weeks after supplement administration. Twelve weeks after supplement administration, HAM-D17 was 8.6±6.3 in responders and was significantly low compared to 18.8±5.1 in non-responders (P=0.02). As shown in Table 1, no difference was seen in age and the duration of disorder between responders and non-responders.

Cortisol in saliva

As shown in Figure 1B, at the start, cortisol levels in saliva were significantly (P=0.03) high compared with normal controls. There was no significant difference in the salivary cortisol level between the responders and non-responders at the start of supplement administration. In non-responders the levels of salivary cortisol continued to be significantly (P<0.05) high except 8 weeks after supplement administration, while in responders the levels of salivary cortisol were normalized after supplement administration. As shown in Figure 2A, in the results of measurements immediately, one hour, two hours, 3 hours and 4 hours after waking up in the morning, the peak value was not seen at waking up in 6 of 8 subjects before the responders began to use the supplement, but 12 weeks later the peak value was seen immediately after waking up in all subjects. In the control group, the peak was seen in 12 of 15 immediately after waking up. The difference between responders at the start and the control group was clear although it was not possible to compare using the chi-square test because there were only 2 subjects in whom the peak was seen immediately after waking up. The results after 12 weeks were not significantly (P=0.01) different from the control group. On the other hand, as shown in Figure 2B, in most of the non-responders the peak value was not seen immediately after waking up, not only before but also after supplement administration. The difference from the control group is clear although the chi-square test could not be performed.

Following the administration of the supplement for 12 weeks, depressive symptoms were significantly alleviated, or the salivary cortisol level decreased to the normal level and a regular circadian rhythm was resumed, in the responder group, whereas depressive symptoms and salivary cortisol level and circadian rhythm did not improve in the non-responder group.

Discussion and Conclusions

From the results of the present study, it is thought that PS and omega-3 fatty acid-containing supplement is effective in a particular group of depressed elderly people. Maggioni *et al.*[13] reported that PS at 300 mg/day for 30 days was administered and was effective in ten elderly women. No change was seen in amine metabolites. Brambilla *et al.*[14] also reported that PS at 300 mg/day for 30 days was administered and was effective in ten elderly women. They reported that PS did not modify the T-lymphocyte response to phytohemoaggulutinin.

Table 1. Profile of supplement responders and non-responders.

	Responders (n=8)	Non-responders (n=10)
Male	6	4
Female	3	5
Age (y)	67.9±3.2	68.5±3.2
Duration of disorder	8.4±2.2	7.2±3.5

Thus, there are a few reports indicating that PS is effective against late life depression, but no reports found any biological changes corresponding to the improvement of depression. The present results correspond to these reports regarding the effectiveness of PS to depression. Neither the amine metabolite nor the immune function was measured in this study but basic levels and the circadian variation of cortisol in saliva were examined. Hyperfunction and dysregulation of the HPA axis are often seen in depression.[21] No report has indicated that such biological abnormality in depression is improved by PS. Regarding the HPA axis, in young, healthy males PS can improve the process of coping with stress. Two double-blind trials established that in young, healthy male athletes subjected to heavy exercise regimens, PS reduced cortisol production while controlling muscle soreness and other aspects of overtraining.[22,23] In elderly men, PS partially restored thyroid-stimulating hormone and prolactin secretion rhythm.[13] The cortisol levels in the present study may have improved along with the improvement of depression or indicate that PS-containing supplement can improve the dysregulation of neuroendocrine function. Because this research targets the elderly, it could be thought that they initially had a cognitive disorder and its improvement by PS appears to be an improvement of depression; however, the subjects in the present study did not have a cognitive disorder. Regarding whether the effect of PS on the elderly is an effect on cognition or on depression, because the effect is detected in the forced swim test which is designed to assess antidepressant effects, and not seen in the maze test which is designed to assess cognitive functions, it is thought that PS is not a cognitive enhancer but an antidepressive enhancer.[24]

The following possibilities were identified in the current report regarding the action mechanism of PS: i) Action on the cell membrane; ii) action on neurotransmitters. The lipid composition of the cell membrane changes with aging; that is, phosphorus lipid decreases while cholesterol increases.[25] As a result, because the normal viscosity of the cell membrane changes, many membrane-bound enzymes and transport systems are affected and the mechanism of enzymatic activity and

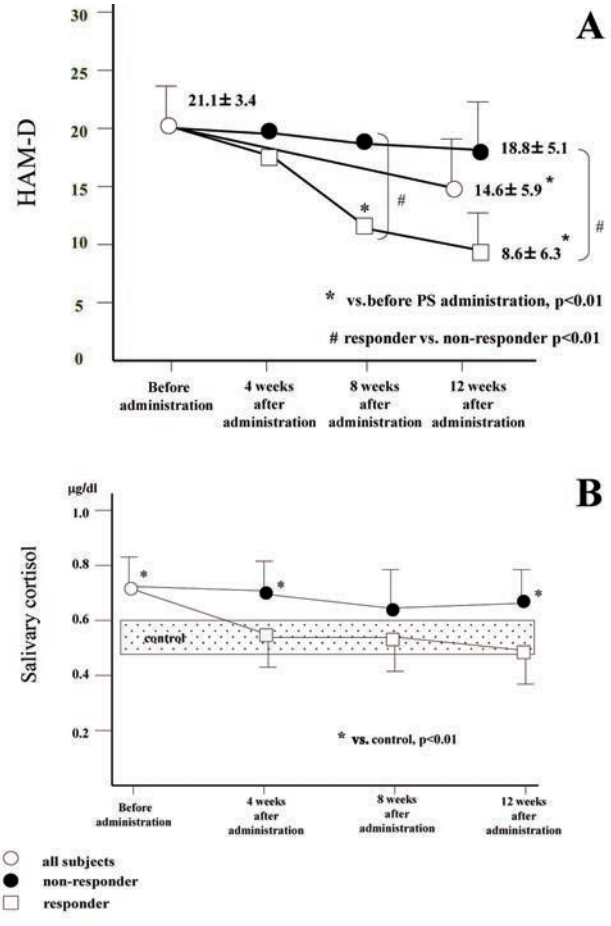

Figure 1. Changes in (A) HAM-D17 by supplement administration and (B) salivary cortisol levels.

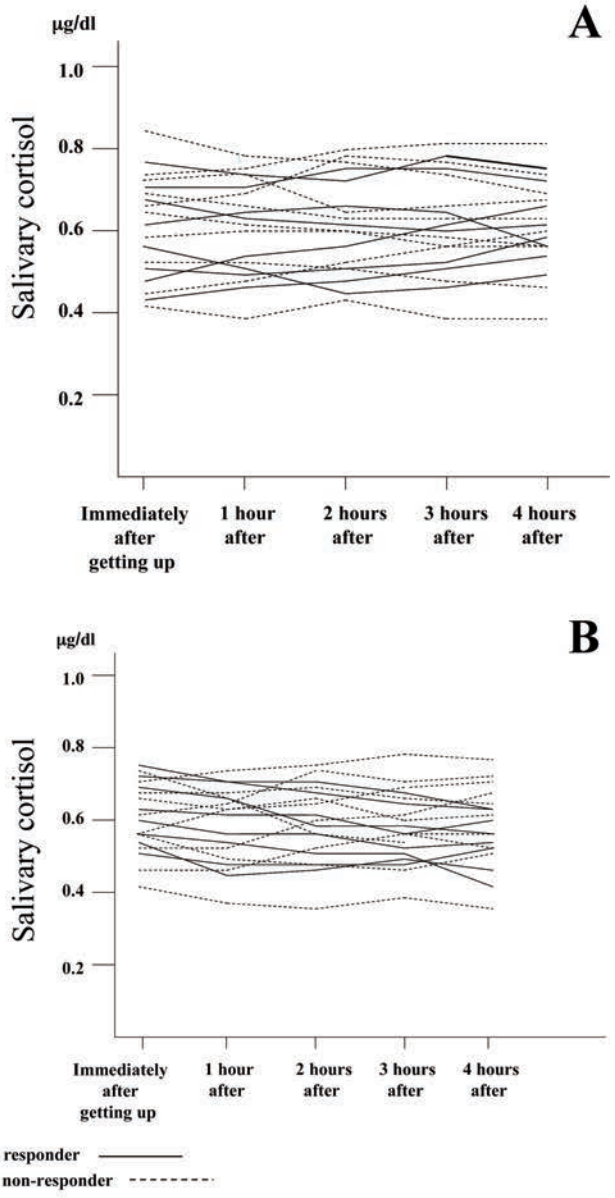

Figure 2. Circadian rhythm of salivary cortisol at the beginning of PS administration (A) and after administration for 3 months (B).

transportation is disrupted.[26,27] As a result, the functions of the brain and the memory, etc. deteriorate. PS activates PKC, an enzyme that contributes to the signal transmission cascade by neurotransmitters in the neurons of the aged rat cerebral cortex.[28] ATPase is also activated by PS.[29,30] ATPase adjusts sodium/potassium balance and calcium/magnesium balance between within and outside the cell and it is thought that the excitability of neurons and transmission of messages in the cell are maintained by administering PS. Decrease of the neurons that produce neurotransmitters is prevented by administering PS and, in particular, it is said that maintenance of the amount of acetylcholine is one mechanism in which PS is useful for cognition syndrome.[31-34] There is a report that the discharge of dopamine is recovered by PS.[35] PS also improves neurotransmission by glutamic acid.[36] Such effects on neurotransmission might be related to its effect on depression. It is reported that reduction of the total volume of neurons and neuronal loss occur in depression.[37] Chronic PS administration recovered dendritic spine loss in the hippocampus of aged rats,[38] and such beneficial effect of PS treatment on neuronal connectivity might be related to the antidepressive effect of PS.

Because components other than PS are included in the supplement used, it cannot be said that the present results are an effect of PS alone. Omega-3 fatty acid DHA and EPA are anchored by phospholipid molecules, including PS, and together with phospholipids and membrane antioxidants function to protect neurodegeneration.[15] Omega-3 fatty acids are involved in a variety of processes in neural cells and their role is far more complex than simply influencing the cell membrane.[39] Although it is not clear whether this occurred in relation to membrane function, omega-3 fatty acids had a beneficial effect on preventing the development of depression-like behavior in rats in the forced swimming test;[40] therefore, omega-3 fatty acids may play an important role in the present results.

Astaxanthin and palm oil-derived tocotrienol may also be involved in the present results. Astaxanthin can cross the brain-blood barrier and is strongly suggested to be effective against oxidative neurodegeneration.[41] Palm oil-derived tocotrienol is natural vitamin E and current studies demonstrate that tocotrienol has neuroprotective properties.[42,43] Arachidonic acid, one of the most abundant polyunsaturated fatty acids, is highly susceptible to oxidative metabolism under pathologic conditions and tocotrienol at nanomolar concentrations was shown to attenuate arachidonic acid metabolism and neurodegeneration;[43] therefore, it seems that elements in addition to PS and omega 3-fatty acids are also important. Clinically, the usual drug therapy for elderly depression does not often succeed and is prolonged. The results of the study suggest that an elderly group with depression responded to the supplement, but not treatment, which may be a significant finding. However, there were no significant differences in the symptoms or cortisol levels between the responders and non-responders at the initiation of its administration, and the paper did not provide any recommendations on the use of supplements by specific patients with depression. At present, the administration of supplements to the elderly with persistent depression is only an option. It is presumed that any change in the brain with aging might contribute to this condition and the supplement might improve neuron function. I will conduct further research to analyze the symptoms in detail and generate biological data other than on cortisol levels, as well as brain imaging.

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