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ORIGINAL ARTICLE

Association between serum oxytocin levels and depressive state in community-dwelling older adults: A cross-sectional study

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Abstract

Aim: Identifying peripheral biomarkers related to the prevention or modification of unhealthy mental conditions in older adults would be extremely beneficial. This study aimed to evaluate serum oxytocin levels in older adults living in a rural community and their association with cognitive function, anxiety, depressive state, and well-being.

Methods: This survey was conducted between November 2016 and September 2017 in Kurokawa-cho, Imari, Saga Prefecture, Japan, among people aged ≥65 years. Blood samples were collected from the participants for serum oxytocin level analysis, which was performed using peptide enzyme immunoassay. Participants underwent neuropsychological assessments, including the Mini-Mental State Examination, Clinical Dementia Rating, Frontal Assessment Battery, State-Trait Anxiety Inventory, 15-item Geriatric Depression Scale, and 17-item Philadelphia Geriatric Center Morale Scale. We examined the association between serum oxytocin levels and neuropsychological assessment results.

Results: Out of 94 participants, 25 were men and 69 were women, with mean ages of 78.24 ± 3.85 years and 78.10 ± 5.43 years, respectively. Serum oxytocin levels were negatively associated with 15-item Geriatric Depression Scale scores. Additionally, nondepressive state/depressive state was classified by the 15-item Geriatric Depression Scale (cut-off 5/6). Logistic regression analysis showed that higher serum oxytocin levels tended to be associated with a less depressive state at that time.

Conclusions: Serum oxytocin levels may be associated with depressive state in adults aged ≥65 years.

KEYWORDS

depressive state, GDS, mental health, older adults, oxytocin

INTRODUCTION

According to Japan's Ministry of Health, Labor and Welfare, Japan has one of the longest life expectancies in the world, and extending healthy life expectancy has become an important issue with the aging population. In 1990, local doctors, public health nurses, and volunteers started a dementia prevention project for general residents in Kurokawa-cho, Imari, Saga Prefecture, Japan. Since 1994, brain magnetic resonance imaging examination, cognitive function assessment, and neuropsychological assessment have been performed for the older adults, and lectures and gymnastics have been conducted in health classes. We have been participating in this project since 2004, longitudinally investigating older adults and conducting research on the existence of highly reliable biomarkers that indicate future risk of cognitive decline and depression. We have been researching how older adults can maintain their mental health while living in a familiar community. To date, we have conducted many epidemiological studies in older adults living in rural communities and identified peripheral biomarkers associated with the maintenance of mental health in them.[1–7] In this study, we focused on oxytocin, which has been implicated in human relationships. It is a pituitary hormone that promotes labor through the contractile action of the uterine muscle and causes a milking reflex during breastfeeding.[8] Research on oxytocin is progressing, and there is evidence that intranasal administration of oxytocin can increase trustworthiness.[9,10] Additionally, oxytocin has been suggested to enhance human social cognition,[11] attachment to others[12,13] and the promotion of cooperation.[14,15] This suggests that oxytocin is deeply involved in maintaining human relations and social cognitive abilities. Moreover, we found a positive association between serum oxytocin levels and logical memory delayed recall.[5] Also, serum oxytocin levels in older adults were positively associated with left hippocampus and amygdala volumes after 7 years.[4] The limbic system, including the hippocampus and amygdala, is an important component of cognitive function necessary for social life.[16–18] These findings suggest that oxytocin may be associated with cognitive function in older adults. A recent report also suggested that intracerebroventricular administration of oxytocin in Alzheimer's disease (AD) model mice improved cognitive behavioral disorders.[19] Additionally, oxytocin is supposed to have various anti-aging effects as it is involved in reducing oxidative stress and inflammation,[20] bone formation and osteoporosis improvement,[21] and muscle regeneration.[22] In view of these reports, we believe that oxytocin is closely related to mental and physical health in older adults. This study evaluated serum oxytocin levels in older adults living in a rural community and examined their association with neuropsychological assessments such as cognitive function, anxiety, depressive state, and well-being. If this study revealed an association between serum oxytocin levels and neuropsychological assessments, it might strengthen the evidence that serum oxytocin levels are one of the peripheral biomarkers related to the prevention or modification of mentally unhealthy conditions in older adults, therefore investigating the association between serum oxytocin levels and neuropsychological assessments in older adults would be beneficial for people in having a social and healthy life.

METHODS

Participant characteristics and survey procedure

This survey was conducted between November 2016 and September 2017 in Kurokawa-cho, Imari, Saga Prefecture, Japan, among people aged ≥65 years, as reported previously.[1–7] Kurokawa-cho is a rural town in northwestern Saga Prefecture that is somewhat cut off from urban areas. As of 2016, the population of Kurokawa-cho was 3137, with 935 (29.8%) people aged ≥65 years. Approximately 100 participants were considered as a sample for the study. The power analysis showed that this sample size resulted in the medium effect size. The participants for this study were basically recruited from a list of participants from past surveys that were part of a longitudinal study. In addition, older people who had not participated in past surveys and intended to take part in this survey were also recruited. When recruiting, sex ratio, cognitive function at that time, and activities of daily living of participants were not considered. We asked a care manager belonging to Kurokawa-cho's in-home nursing care support project to confirm whether participants could cooperate with the study. Ninety-seven participants then agreed to participate in the survey. Surveys were conducted once a week, with three participants surveyed each day. The data contained 84 older adults who participated in the previous surveys and 13 older adults who were new participants. During the survey, two participants arbitrarily dropped out of the study, resulting in 95 completing the survey. One participant with serum oxytocin levels higher than three standard deviations was excluded, so a cross-sectional analysis was performed on 94 participants.

All methods of this study were carried out in accordance with the guidelines of the Declaration of Helsinki and were approved by the Ethics Committee of the Faculty of Medicine, Saga University, Japan and written informed consent was obtained prior to participation of all participants.

Neuropsychological assessments

All participants underwent neuropsychological assessment to evaluate various cognitive function, anxiety, depressive state, and well-being. The Mini-Mental State Examination is a simple screening index that estimates cognitive function.[23] The Clinical Dementia Rating (CDR) is used for dementia evaluation and severity staging.[24,25] The Frontal Assessment Battery is a subtest that measures different cognitive functions related to the frontal lobe.[26] The State-Trait Anxiety Inventory is a psychological test that measures anxiety.[27] The 15-item Geriatric Depression Scale (GDS) is one of the most widely used screening instruments for depressive state among older

adults; it consists of 15 items and does not include items related to physical symptoms.[28] The 17-item Philadelphia Geriatric Center Morale Scale is a measure of subjective well-being in older adults.[29]

Serum samples

Blood samples for serum oxytocin levels were collected from the participants between 13:00 and 15:00. On the same day, all samples were centrifuged at Saga University. Next, serum was extracted, transferred to a container, and immediately stored at −80°C.

Serum oxytocin assay

The serum was thawed to room temperature. All samples were analyzed in duplicate. Serum oxytocin levels were measured using a commercially available peptide enzyme immunoassay (Peninsula Laboratories International) without extraction procedure as reported previously.[3–5,30–32] The protocol for this assay recommends sample extraction prior to using kits. Additionally, the kit may still be used without extraction but this may cause unexpected results due to the possible binding between serum proteins and kit components. A robust correlation has been reported between extracted and unextracted serum oxytocin levels.[33] However, the debate on sample extraction before oxytocin assay[34] is important. In our study, the inter-assay and intra-assay coefficients of variation were 9.77%, and 12.98%, respectively.

Statistical analysis

All statistical analyses were conducted using JMP statistical software (JMP 16.1.0; SAS Institute). Descriptive statistics was computed as mean and standard deviation (mean ± SD). Mean values were compared using Welch's *t*-test. Fisher's exact test was used to compare CDR. Multiple regression analysis was used to examine the association between serum oxytocin levels and neuropsychological assessment results. Neuropsychological assessments were used as outcomes and analyses were performed for each indicators. In the analysis, serum oxytocin levels were used as the independent variable and Model 1 was unadjusted, Model 2 was adjusted for age, and Model 3 was adjusted for age and sex. Statistical significance was set at $P < 0.05$.

RESULTS

A total of 94 older adults were included in the study, out of which 25 were men and 69 were women. The mean ages of men and women were 78.24 ± 3.85 and 78.10 ± 5.43 years, respectively. There was no significant difference in the serum oxytocin levels between men (81.28 ± 62.53 pg/ml) and women (94.18 ± 65.27 pg/ml). Furthermore, no significant difference was seen between men and women in years of education or neuropsychological assessments (Table 1). We adjusted for age and sex, and analyzed the association between serum oxytocin levels and neuropsychological assessments, excluding CDR, by multiple regression analysis. The results showed that serum oxytocin levels were negatively associated with GDS scores (Table 2). However, no association was observed between serum oxytocin levels and other neuropsychological assessments. Additionally, nondepressive state/depressive state was classified by GDS (cut-off 5/6), and logistic regression analysis was performed on the association with serum oxytocin levels. The results showed that those with higher serum oxytocin levels tended to be in a less depressive state at that time (Table 3).

DISCUSSION

In this study, we focused on the association between serum oxytocin levels and neuropsychological assessments in people ≥65 years. Serum oxytocin levels were negatively associated with GDS, with a statistically significant difference even after adjusting for age and sex. In our previous studies, we observed that serum oxytocin levels were positively associated with logical memory delayed recall[5] and were positively associated with hippocampal and amygdala volumes 7 years later.[4] These findings suggest that oxytocin may be associated with cognitive function in older adults. Oxytocin may be one of the indicators for predicting cognitive decline in advance or one of the factors leading to the prevention of dementia in older adults. A recent report suggested that intracerebroventricular administration of oxytocin in AD model mice improved cognitive behavioral disorders.[19] Given that depression is associated with development of AD and dementia,[35,36] and given the findings of our previous oxytocin study,[4,5] association between oxytocin and depressive state may have been somewhat predictive. Oxytocin interacts with various neurotransmitters and neuroendocrine systems.[37] The prominent ones are the serotonergic and gamma-aminobutyric acid-ergic systems and the hypothalamic–pituitary–adrenal axis. Oxytocin modulates the endocrine stress response.[38,39] Increased oxytocin release in the paraventricular nucleus of the hypothalamus in response to stress was observed.[40] One of the biological mechanisms by which higher oxytocin results in a lower depressive state may be due to this process, which is assumed to downregulate neuroendocrine stress responses.

On the GDS, each score is summed to give a total score from 0 to 15, with a score of 6 or higher possibly indicating a depressive state. A higher score indicates a more depressive state. Previous reports have also found decreased blood oxytocin levels in patients with depression.[41] The study of adults, including an age range of up to 65 years, showed that serum oxytocin levels were lower in patients diagnosed with depression when compared to healthy controls.[42] In postpartum depression, plasma oxytocin levels have been shown to be inversely related to depressive symptoms.[43] The study in older

TABLE 1 Participant demographics.

	Overall	Men	Women	*P*
N	94	25	69	
Age (years), mean ± SD	78.14 ± 5.04	78.24 ± 3.85	78.10 ± 5.43	0.891[a]
Oxytocin (pg/ml), mean ± SD	90.75 ± 64.48	81.28 ± 62.53	94.18 ± 65.27	0.387[a]
Education (years), mean ± SD	9.99 ± 1.90	10.56 ± 2.20	9.78 ± 1.75	0.120[a]
BMI (kg/m^2), mean ± SD	23.90 ± 3.53	23.83 ± 3.04	23.92 ± 3.71	0.908[a]
MMSE, mean ± SD	27.07 ± 2.99	26.84 ± 2.94	27.16 ± 3.03	0.647[a]
FAB, mean ± SD	13.67 ± 2.78	13.68 ± 3.08	13.67 ± 2.69	0.985[a]
STAI trait, mean ± SD	38.98 ± 8.34	38.64 ± 9.15	39.10 ± 8.09	0.825[a]
STAI state, mean ± SD	39.77 ± 9.02	37.46 ± 8.50	40.59 ± 9.11	0.135[a]
GDS, mean ± SD	2.86 ± 2.54	3.16 ± 3.09	2.75 ± 2.32	0.553[a]
PGCMS, mean ± SD	12.07 ± 3.26	12.24 ± 3.54	12.01 ± 3.18	0.781[a]
CDR, *n* (%)				
0	85 (90.4)	22 (88.0)	63 (91.3)	
0.5	8 (8.5)	3 (12.0)	5 (7.25)	
1	1 (1.1)	0 (0)	1 (1.45)	
0.5 or more	9 (9.6)	3 (12.0)	6 (8.7)	0.696[b]

Note: Missing data: STAI state (*N* = 2).

Abbreviations: BMI, body mass index; CDR, Clinical Dementia Rating; FAB, Frontal Assessment Battery; GDS, 15-item Geriatric Depression Scale; MMSE, Mini-Mental State Examination; PGCMS, 17-item Philadelphia Geriatric Center Morale Scale; STAI, State-Trait Anxiety Inventory.

[a]Welch's *t*-test.

[b]Fisher's exact test.

adults with sarcopenia obesity observed a trend toward a lower depression score with intranasal oxytocin administration.[44] In our current study, we examined only older adults and observed an association between serum oxytocin levels and depressive state. Our cross-sectional results may be novel, although it may be difficult to prove a causal relationship between oxytocin and depressive state in the older adults. Oxytocin may be useful in the future as a numerical indicator for evaluating depressive state.

Regarding associations with indicators other than depression, one study showed an inverse relationship between plasma oxytocin levels and the severity of symptoms of depression and anxiety in depressed patients.[45] However, this study was in nonolder participants. Also, one study showed a positive relationship between state anxiety and oxytocin in healthy premenopausal women.[46] In addition, plasma oxytocin levels were positively correlated with overall quality of life, psychological health, and social relationships in 60 patients with major depressive disorder and 60 healthy controls.[47] The participants of this study were adults aged 18–69 years. It may be difficult to simply compare between our study and these studies because of differences in the age and number of participants. Additionally, plasma levels of oxytocin in resting subjects can vary by 33%–51%,[48] and the stress associated with venipuncture may confound the reliance on a single time point.[49] Although only an association between oxytocin and GDS scores was found in this study, the importance of repeated measurements of oxytocin may also need to be considered.

Older age may be a time when people are more likely to become depressed because of the increase in life events such as changes in physical functions, loss of social roles, and bereavement of spouses and siblings. Depression may also be the most common unhealthy psychological condition among older adults. Moreover, post COVID-19 pandemic, the prevalence of depression and anxiety among older adults has increased,[50] and the stressors associated with the pandemic may not be measurable. The secretion of oxytocin, which may contribute to the prevention of depression and dementia and delay the onset of dementia, can be promoted in one's daily life. For example, oxytocin secretion is increased by acts of kindness toward others, such as supporting a partner or others in need, or having a close connection with those people.[51,52] Further studies are required to evaluate the effect of oxytocin in the prophylaxis and treatment of depression and dementia. However, it is possible for older adults to take action to prevent depression and dementia by themselves to maintain their mental health. Providing evidence-based information and educating people about the relationship between oxytocin and mental health may lead to behavioral change, contributing to a healthy state of mind.

This study has some limitations. It was a cross-sectional study and the association between serum oxytocin levels and GDS requires

TABLE 2 Multiple regression analysis with neuropsychological assessments as the outcome variable.

		Model 1: Unadjusted				Model 2: Adjusted for age				Model 3: Adjusted for age and sex			
		Estimate	SE	β	P	Estimate	SE	β	P	Estimate	SE	β	P
Outcome: MMSE													
	Oxytocin	0.005	0.005	0.113	0.278	0.002	0.004	0.039	0.684	0.002	0.004	0.035	0.713
	Age, years					−0.267	0.056	−0.450	<0.0001	−0.267	0.056	−0.450	<0.0001
	Sex (women)									0.131	0.316	0.039	0.681
Outcome: FAB													
	Oxytocin	0.006	0.004	0.147	0.158	0.005	0.004	0.107	0.296	0.005	0.004	0.109	0.295
	Age, years					−0.132	0.056	−0.239	0.022	−0.132	0.057	−0.238	0.023
	Sex (women)									−0.046	0.318	−0.015	0.885
Outcome: STAI Trait													
	Oxytocin	0.002	0.013	0.018	0.863	0.001	0.014	0.011	0.914	0.001	0.014	0.009	0.931
	Age, years					−0.065	0.176	−0.040	0.711	−0.066	0.177	−0.040	0.712
	Sex (women)									0.218	0.992	0.023	0.826
Outcome: STAI state													
	Oxytocin	0.007	0.015	0.051	0.633	0.005	0.015	0.034	0.748	0.002	0.015	0.016	0.880
	Age, years					−0.177	0.192	−0.099	0.358	−0.182	0.191	−0.101	0.344
	Sex (women)									1.542	1.077	0.151	0.156
Outcome: GDS													
	Oxytocin	−0.011	0.004	−0.281	0.006	−0.010	0.004	−0.261	0.011	−0.010	0.004	−0.259	0.013
	Age, years					0.059	0.051	0.116	0.254	0.059	0.051	0.116	0.255
	Sex (women)									−0.134	0.288	−0.047	0.643
Outcome: PGCMS													
	Oxytocin	−0.007	0.005	−0.132	0.205	−0.007	0.005	−0.144	0.173	−0.007	0.005	−0.143	0.182
	Age, years					−0.049	0.068	−0.076	0.470	−0.049	0.068	−0.076	0.473
	Sex (women)									−0.070	0.384	−0.019	0.857

Abbreviations: SE, standard error; β, standardized partial regression coefficient.

TABLE 3 Logistic regression analysis with GDS (cut-off 5/6) as the outcome variable and serum oxytocin levels as the independent variable.

	OR	Lower 95% CI	Upper 95% CI	P
Model 1: Unadjusted	0.989	0.978	1.000	0.031
Model 2: Adjusted for age	0.989	0.978	1.000	0.040
Model 3: Adjusted for age and sex	0.989	0.978	1.000	0.046

Note: For the odds ratio of depressive state versus nondepressive state.
Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio.

further analysis using longitudinal data. The effects of diurnal variation[53] on serum oxytocin levels may have been controlled to some extent by collecting blood samples between 13:00 and 15:00. However, details about activities[54] and diet[55] prior to survey were not obtained. Older people may often take a variety of medications, including hormonal agents for physical diseases. However, details about these medications were not obtained. The effects of these factors on oxytocin levels could not be measured. Additionally,

lifestyles such as activities and diets, and the social connections of older people may differ in rural and nonrural regions, and their effects on oxytocin levels may also differ, therefore the current results may not be generalizable to nonrural regions. Serum oxytocin levels were measured using a commercially available peptide enzyme immunoassay following an extraction-free protocol. Oxytocin measurements using enzyme-linked immunosorbent assay have been discussed in several studies. Extraction removes interfering substances.[56] However, discarded substances may include oxytocin bound to proteins.[57] A robust correlation has been reported between extracted serum oxytocin levels and unextracted serum oxytocin levels,[33] therefore the debate on sample extraction before oxytocin assay[34] is important. The results of measurements by this method may be preliminary for that reason. Furthermore, the relationship between peripheral and central oxytocin levels is an ongoing debate, and even though positive correlation between them has been reported,[58] there are reports that there is no significant association between peripheral and central concentrations.[59]

In conclusion, we have focused on the association between serum oxytocin levels and neuropsychological assessments in older adults living in rural communities. We found that for people aged ≥65 years, serum oxytocin levels were negatively associated with GDS scores. This result suggests that serum oxytocin levels may be associated with depressive state in adults aged ≥65 years.

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AUTHOR CONTRIBUTIONS

R.O., Y.I., S.Y., A.M., and Y.M. designed this study. R.O., Y.I., and Y.M. acquired the data. R.O. analyzed data. R.O. drafted and Y.M. edited this manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (Yoshito Mizoguchi) but restrictions apply to the availability of these data due to the restriction under the institutional ethical committee's policy and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the corresponding author (Yoshito Mizoguchi).

ETHICS APPROVAL STATEMENT

All methods of this study were carried out in accordance with the guidelines of the Declaration of Helsinki and were approved by the Ethics Committee of the Faculty of Medicine, Saga University, Japan.

PATIENT CONSENT STATEMENT

Written informed consent was obtained prior to participation of all participants.

CLINICAL TRIAL REGISTRATION

N/A.

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