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SHORT COMMUNICATION

Back massage therapy promotes psychological relaxation and an increase in salivary chromogranin A release

Yuka Noto · Mihoko Kudo · Kazuyoshi Hirota

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Abstract Massage therapy promotes psychosocial relaxation, reduces stress and has been reported to improve the immune function. As such, massage therapy is currently used in palliative care for the relief of anxiety and pain. Although psychosocial status has been evaluated using subjective psychological tests, such as State-Trait Anxiety Inventory (STAI), subjective psychological tests are of limited value if the subjects fail to report reliably. Salivary biomarkers have been recently suggested as useful objective markers for assessing psychosocial status. To determine whether salivary biomarkers are useful objective indices for assessing the effects of back massage on the mental status of 25 young healthy female volunteers, we measured heart rate and salivary biomarkers (α-amylase activity, cortisol, and chromogranin A) and assessed the STAI score before and after the back massage. Back massage significantly reduced the heart rate and STAI; however, salivary amylase and cortisol levels did not change. In contrast, the level of salivary chromogranin A significantly increased. We therefore conclude that changes in the salivary biomarkers tested here may not indicate changes in psychological status following massage therapy. However, the increase in chromogranin A release may contribute to the immunologically beneficial effects of massage therapy as chromogranin A has antibacterial and antifungal activity.

Y. Noto
Department of Nursing, Hirosaki University Graduate School of Health Sciences, Hirosaki 036-8563, Japan

M. Kudo · K. Hirota (✉)
Department of Anesthesiology, Hirosaki University Graduate School of Medicine, Hirosaki 036-8563, Japan
e-mail: hirotak@cc.hirosaki-u.ac.jp

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Massage therapies have been reported to produce beneficial physiological effects, such as vasodilation, an increase in skin temperature, and body relaxation [1]. The underlying mechanisms are still unknown, but it has been hypothesized that a reduction in lactic acid build-up in muscles, improved lymphatic and venous circulation, and stimulation of the healing of connective tissues may be involved [1]. Massage has also been proposed to promote psychosocial relaxation and reduce stress [2]. Consequently, massage therapy is currently used in palliative care for the relief of anxiety and pain [3].

Evaluations of psychosocial stress or mental relaxation have been performed using various subjective psychological tests, such as the State-Trait Anxiety Inventory (STAI) score. However, if the subjects fail to report reliably, subjective psychological tests are of limited value. Therefore, alternative objective assessment methods have been sought. One of the commonest objective measures of stress involves an assay of hormone levels as psychosocial stress activates the hypothalamus–pituitary–adrenocortical (HPA) axis and sympatho-adrenomedullary (SAM) system. Activation of HPA increases cortisol secretion from the adrenal cortex [4]. In the SAM system, plasma norepinephrine is derived both from the spillover of synaptic norepinephrine in the sympathetic nervous system and from the adrenal medulla, while plasma epinephrine is derived mainly from the adrenal medulla. Therefore, plasma cortisol and catecholamine concentrations would reflect stress status. However, blood sampling alone (with concomitant pain and stress) may also increase these stress

hormone levels. Recently, measurements of salivary cortisol, α-amylase activity, and chromogranin A have been evaluated as stress biomarkers [4–7] since salivary sampling can be performed under noninvasive and nonstressful conditions. Based on the results of an earlier study, we also reported that salivary α-amylase activity may reflect both mental arithmetic stress and chronic pain [8, 9].

Salivary cortisol increases with psychological stress and correlates with serum cortisol [5], salivary α-amylase is associated with changes in plasma norepinephrine under exercise and psychosocial stress [6], and chromogranin A is subject to exocytotic co-release with catecholamines from both the adrenal medulla and adrenergic neurons [10]. Kanamaru et al. [7] found that salivary chromogranin A is a sensitive maker of the initial psychological phase of the stress response. Therefore, these salivary biomarkers may be useful indicators for assessing psychosocial stress status.

In the study reported here, we determined whether salivary biomarkers are useful objective indices for assessing the effects of back massage on mental status.

The university ethics committee approved the study, and informed consent was obtained from the 25 healthy female students of The Department of Nursing, Hirosaki University School of Health Sciences (age range 21–23 years, mean age 21.8 ± 0.6 years) who participated in the study. The volunteers completed questionnaires prior to enrollment in the study confirming the absence of physical or mental illness, the use of any medication affecting the autonomic nervous and endocrine systems, and the absence of severe periodontal disease causing a tendency to gingival bleeding. The subjects were instructed to abstain from eating and drinking any beverages except water and from brushing their teeth 1 and 3 h before the experiment.

The experiments were performed between 1300 and 1800 hours to minimize any circadian rhythm effects. After the volunteers had rinsed their mouth with water and an electrocardiogram was recorded, they rested in a chair for 10 min. All volunteers then received the same standardized massage of the back for 10 min with non-aromatic oil.

We used the Japanese translation of the state section of STAI to assess the response to anxiety. Each subject completed this section, and the state anxiety score (STAI score) was calculated before and 0 and 30 min after the massage.

Saliva was collected with a cotton swab into special sampling tubes (Salivettes; Sarstedt, Nümbrecht, Germany). The tubes were then centrifuged for 3 min at 1500 *g* to obtain clear saliva, which was stored at –80°C until assay. Salivary chromogranin A and cortisol were assayed using an enzyme immunoassay kit according to the manufacturers instructions (YKO70 Human Chromogranin A, EIA kit, Yanaihara Institute, Shizuoka, Japan; Salivary Cortisol EIA kit, Salimetrics, State College, PA). Salivary α-amylase activity was assayed using a commercial kit according to the manufacturer's instructions (Salivary α-Amylase Assay kit, Salimeterics). Chromogranin A levels were corrected for salivary protein, which was determined using the Bio-Rad Protein Assay kit (Bio-Rad, Hercules, CA) and expressed as picomoles per milligram protein. The intra-assay maximal coefficient of variation was 8.2% for chromogranin A, 6.2% for cortisol, and 6.7% for α-amylase. The inter-assay maximal coefficient of variation was 12.4% for chromogranin A, 6.9% for cortisol, and 5.8% for α-amylase.

Data are presented as the mean ± standard deviation. Statistical analysis was performed using one-way repeated measures analysis of variance (ANOVA) followed by the Student–Newman–Keuls test using GraphPad Prism V3 (GraphPad Software, San Diego, CA). A $p < 0.05$ was considered significant.

Heart rate and STAI score decreased significantly after back massage (Fig. 1). However, salivary amylase and

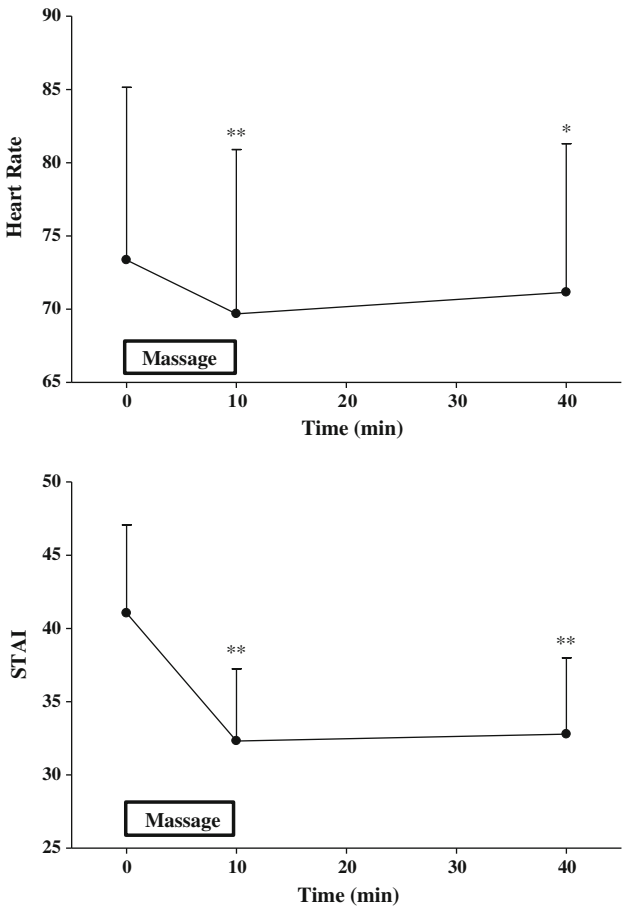

Fig. 1 Effects of back massage on heart rate (**a**) and State-Trait Anxiety Inventory (STAI) score (**b**). Values are given as the mean ± standard deviation: *0 min* before massage therapy, *10 min* just after massage therapy finished, *40 min* 30 min after completion of massage therapy. *$p < 0.05$ vs. 0, **$p < 0.01$ vs. 0

Table 1 Effects of back massage on salivary chromogranin A, α-amylase activity, and cortisol levels

Salivary biomarker	Time (min)[a]		
	0	10	40
Chromgranin A (pmol/mg protein)	2.93 ± 2.21	5.29 ± 5.46*	4.46 ± 5.11
α-Amylase activity (U/ml)	60.5 ± 39.8	54.5 ± 38.7	73.5 ± 57.6
Cortisol (μg/dl)	0.173 ± 0.149	0.195 ± 0.227	0.167 ± 0.168

Data are given as the mean ± standard deviation

*$p < 0.05$ vs. time 0

[a] 0 min, Before massage therapy; 10 min, just after massage therapy finished; 40 min, 30 min after completion of massage therapy

cortisol levels did not change (Table 1). In contrast, salivary chromogranin A level increased significantly just after completion of the massage (Table 1).

Our results show that the levels of the three salivary biomarkers tested, α-amylase, cortisol, and chromogranin A, did not decrease despite the reductions in STAI and heart rate, which were a direct result of the massage and indicative of mental relaxation. Therefore, these salivary biomarkers may not reflect changes in psychological status produced by massage therapy. However, these salivary biomarkers have been reported to reflect psychological stress. Nakane et al. [4] reported that the level of salivary chromogranin A significantly increased during a word processing task. Chatterton et al. [6] reported that salivary α-amylase activity is associated with changes in plasma norepinephrine concentrations under exercise and psychosocial stress. Rohleder et al. [11] also showed a positive association between increases in α-amylase activity and plasma norepinephrine induced by psychosocial stress as measured with the Trier Social Stress Test. In addition, Noto et al. observed that the salivary cortisol level significantly increased in response to psychological stressors [8]. Therefore, these salivary biomarkers may be good indicators for assessing mental stress but not for evaluating mental relaxation.

Circulatory chromogranin A is taken into the salivary glands and then discharged with saliva following activation of the sympathetic nervous system and subsequent innervation of the salivary gland [12]. Thus, we expected that salivary chromogranin A would be reduced by the massage therapy as the massage therapy induces psychological relaxation and reduces the heart rate, which may imply sympatholytic status. However, far from our expectation, salivary chromogranin A levels significantly increased after massage. Although we cannot explain the mechanism, several reports indicate that massage therapy enhances immune functions in cancer patients [2] and improves immune function in human immunodeficiency virus patients [13]. It has also been reported that chromogranin A may have antibacterial and antifungal activities [14, 15]. Vasostantin-1, which is naturally processed from the N-terminal 1-76 of chromogranin A, inhibits the growth of bacteria and fungi [14, 15]. Therefore, massage therapy may increase host defense with salivary chromogranin A release against orally microbial invasion. Similarly, although salivary immunoglobulin A has also been suggested to be a good indicator for assessing mental stress [16], Groër et al. [17] reported that a 10-min nursing back rub increased salivary immunoglobulin A secretion despite an decrease in STAI score. Salivary immunoglobulin A also acts as a first line of host defense against microbial invasion [18]. Therefore, massage therapy may reinforce host defense with an increase in the secretion of antimicrobial peptides, such as chromogranin A and immunoglobulin A.

Assessment of preanesthetic anxiety, surgical stress, and both acute and chronic pain intensity is a very important area of clinical anesthesia research. Several methods for assessing psychological and physiological stress have been established. Although the STAI score and visual analog scale have been recognized as useful subjective assessment tools [19], these tools are of limited value if patients fail to reliably report. Objective assessment methods may be more reliable, and the assay of plasma stress hormone has been used as the most common objective method. However, blood sampling alone may increase stress hormone levels by concomitant pain. This has led to the measurement of salivary biomarkers being used as a non-invasive assessment tool in the clinical anesthesia field [9, 20].

In conclusion, our data suggest that salivary biomarkers may not be good indicators of psychosocial relaxation. Massage therapy increased chromogranin A release, which may contribute to the immunologically beneficial effects of massage therapy.

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