Neuroendocrinology Letters Volume 44 No. 1 2023
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Differences in the diurnal variation of salivary stress biomarkers during the coronavirus (COVID-19) pandemic between telecommuters and office workers.

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Submitted: 2022-11-09 Accepted: 2023-02-13 Published online: 2023-02-13

Key words: **COVID-19 pandemic; cortisol; melatonin; office worker; oxytocin; saliva; stress biomarker; telecommuter**

Neuroendocrinol Lett 2023; **44**(1):26–30 **PMID:** 36931224 NEL440123A03

Abstract

OBJECTIVES: It is necessary to objectively assess the stress state of workers, from the standpoint of holistic palliative care, in order to determine how the rapid change in work styles in the "live with coronavirus era"—in which people will coexist and live with the coronavirus (COVID-19)—will affect their physical and mental health. The aim of this study is to assess the impact of rapid changes in work patterns during the COVID-19 pandemic on the neuroendocrine stress response of workers.

DESIGN AND METHODS: A total of sixteen subjects, 9 telecommuters (2 males, 7 females; age, 37.1±2.6 years) and 7 office workers (3 males, 4 females; age, 37.3±3.0 years) who provided their informed consent were enrolled in this prospective observational study. Saliva was collected four times a day (after waking, noon, evening, and before bedtime) and three times a week (Monday, Wednesday, and Friday) during May and June 2020. The saliva samples were stored at -20°C until measurement. Saliva components were analyzed by ELISA for cortisol, melatonin, s-IgA, and oxytocin.

RESULTS: The diurnal variation of salivary components between telecommuting and office work groups was investigated. Cortisol showed diurnal variation with higher secretion during waking hours and lower secretion toward nighttime in both groups, and no modulation was observed. In the office work group Melatonin showed diurnal variation, with increased secretion at night. In contrast, the telecommuting group showed modulation, with higher secretion at waking and lower secretion at night. s-IgA showed diurnal variation with a high level at waking and a low level thereafter in both groups, and no modulation was observed. The telecommuting group showed higher oxytocin levels in comparison to the office work group.

CONCLUSIONS: These results suggest that the absence of commuting in the telecommuting group reduces anxiety due to infection, and that the diurnal variation of melatonin may be due to the alteration of circadian rhythm caused by being at home all day.

INTRODUCTION

Stress occurs in any environment, whether at work or at home, and people today live in a stress-filled society (Esch & Stefano 2010). Regardless of age or sex, people must control stress in order to fulfill their own lives. However, the spread of the new coronavirus has triggered a major change in the way people work, and there is a growing trend to introduce telecommuting (Awada *et al.* 2021). It is necessary to objectively assess the state of stress from the standpoint of holistic care to see how the rapid changes in work patterns in the "live with coronavirus era," in which people live in harmony and coexist with the new coronavirus, will affect the physical and mental health of those who work.

The major response systems of the biological body's stress system are the endocrine response of the hypothalamic-pituitary-adrenal axis (HPA axis) and the autonomic nervous system response of the sympathetic-adrenal-medullary axis (SAM axis) (Godoy *et al.* 2018). Quantitative evaluation of biomarkers related to the HPA and SAM axes, in combination is important for objective stress assessment. We have been conducting a comprehensive assessment of stress biomarkers using saliva samples as a non-invasive and simple method to assess stress changes (Watanabe *et al.* 2021). Saliva samples are biological samples that can be collected continuously throughout the day and are suitable for the evaluation of biomarkers for which diurnal variation must be considered. In this study, we investigated the effect of diurnal variation on salivary stress markers in order to assess stress-related changes in telecommuters and office workers during the coronavirus pandemic.

Tab. 1. Subjects' characteristics

	Sex	Age	Co-resident
Telecommuters			
1	Female	26	–
2	Female	38	+
3	Female	32	–
4	Female	32	+
5	Male	38	–
6	Female	57	–
7	Female	39	+
8	Male	38	+
9	Female	34	+
Office workers			
1	Female	29	–
2	Female	41	–
3	Female	48	+
4	Male	44	+
5	Male	38	+
6	Male	35	+
7	Female	26	–

MATERIAL AND METHODS

Study Design

After obtaining their written consent, 16 healthy Japanese adults who mainly performed deskwork were enrolled in this prospective observational study from May to June 2020. These individuals included 9 telecommuters (2 males and 7 females; age, 37.1 ± 2.6 years) and 7 office workers (3 males and 4 females; age, 37.3 ± 3.0 years). Saliva was collected four times a day (after waking, noon: 11:00-13:00; evening: 17:00-19:00, and before bedtime), three days a week (Monday, Wednesday, and Friday). A flowchart of the study is shown in Figure 1. All protocols of this study were approved by the review board and ethics committee of Juntendo University, and conformed to the tenets of the Declaration of Helsinki. Informed consent for the measurements was obtained from each of the participants.

Measurement of salivary stress biomarkers

Approximately 1 ml of saliva was collected using a Saliva Collection Aid (SCA: Salimetrics, U.S.A.). The collected saliva was stored at -20°C until measurement. Four salivary stress biomarkers were measured: cortisol, melatonin, s-IgA, and oxytocin. The subject put a straw, which was inserted in a vial (preservation tube), into their mouth, and the saliva was taken into the vial as it dropped. The obtained saliva was stored frozen at -20°C until the analysis of its components. With regard to the salivary components, cortisol, melatonin, s-IgA and oxytocin were measured using a Salivary Cortisol Enzyme Immunoassay Kit (Salimetrics, USA), a Salivary Melatonin Enzyme Immunoassay Kit (Salimetrics, USA), a Salivary Secretory IgA Indirect Enzyme Immunoassay Kit (Salimetrics, USA), and an Oxytocin ELISA kit (Enzo, USA), respectively.

Statistical analyses

Student's *t*-test was used for the comparison of continuous variables and the chi-squared test was used for the comparison of categorical data between two groups. *P* values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the JMP® 16 software program (SAS Institute Inc., Cary, NC, USA).

RESULTS

Characteristics of study participants

Table 1 shows the characteristics of the telecommuters and office workers. The 9 telecommuting

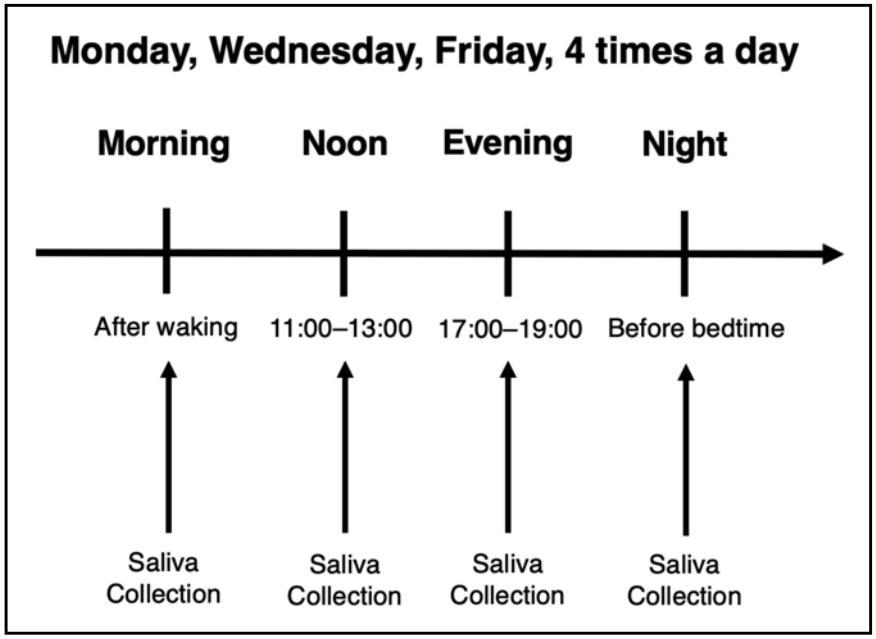

Fig. 1. The study procedure. Saliva samples were collected four times a day (after waking, noon: 11:00-13:00; evening: 17:00-19:00, and before bedtime), three times a week (Monday, Wednesday, and Friday).

workers consisted of 2 males and 7 females (mean age 37.1 ± 2.6 years), and the 7 regular workers consisted of 3 males and 4 females (mean age 37.3 ± 3.0 years). There were no significant differences between the telecommuter and office worker groups in terms of sex ($p = 0.3773$, chi-squared test), age ($p = 0.9673$, Student's *t*-test), or the presence of co-residents ($p = 0.9494$, chi-squared test).

Diurnal variation in salivary stress biomarkers between telecommuters and office workers

Diurnal variation in salivary stress biomarkers was examined in telecommuters and office workers. Cortisol showed diurnal variation in both groups, being higher on waking and lower toward nighttime, and no modulation was observed (Figure 2-A). Melatonin generally shows diurnal variation, with increased secretion at night, but in the telecommuter group, the melatonin level was higher upon waking and lower toward nighttime (Figure 2-B). No modulation of the diurnal variation of melatonin was observed in the office worker group (Figure 2-B). In both groups, s-IgA showed diurnal variation with a high level upon waking and a low level after that, and no modulation was observed (Figure 3-A). Oxytocin was higher in the telecommuter group regardless of the day of the week or day/night (Figure 3-B).

DISCUSSION

This study examined the effects of diurnal variation in salivary stress markers to assess changes in stress among telecommuters and office workers during the coronavirus pandemic. In comparison to the office worker group, the telecommuter group showed a significant change in melatonin, with higher levels upon waking and lower levels toward nighttime. Cortisol, on the other hand, showed no modulation in either group, with a normal diurnal variation of higher levels upon waking and lower levels toward nighttime. This indicates that circadian rhythms are well regulated among office workers who generally have a routine of getting up in the morning, going to work, and going to bed at night. The modulation of the diurnal variation of melatonin suggested that being at home all day modulates circadian rhythms. These results were thought to be due to the fact that telecommuters do not have to travel to work and have fewer opportunities for human contact, which reduced concerns about infection.

Melatonin is a fat-soluble bioactive amine synthesized from tryptophan, an amino acid, via serotonin, and is characterized by secretion at night with suppressed secretion during daylight hours (Chojnowska *et al.* 2021). Thus, it produces a diurnal variation, a circadian rhythm based on the light-dark cycle (Chojnowska *et al.* 2021). Circadian rhythm disturbances often occur during stress, depression or anxiety, and many reports suggest that salivary melatonin concentration could be used as a stress biomarker (Ito *et al.* 2013; Paul *et al.* 2019). Telecommuters who refrain from staying outside during Covid-19 pandemic are forced to remain indoors for long periods of time, alienated from the natural environment, and have less opportunity to be exposed to natural light. In addition, telecommuting expands the range and flexibility of work styles, creating an environment in which employees can work at night without being tied down during the day, as core work hours are less fixed than in normal work hours. The significant difference in melatonin secretion in this study may be related to these factors.

Oxytocin is a peptide composed of nine amino acids and is considered to be one of the most classical

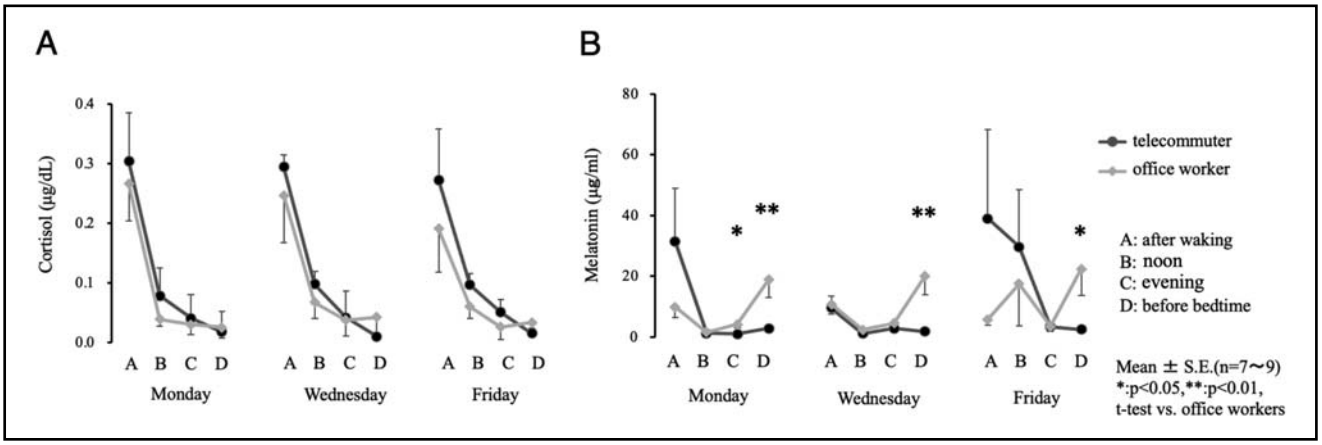

Fig. 2. Changes in salivary cortisol levels (A) and salivary melatonin levels (B)

hormones. It is synthesized by oxytocin neurons in the hypothalamic paraventricular nucleus and supraoptic nucleus, and then is secreted from the posterior pituitary gland. In recent years, in addition to its association with maternal functions—such as labor acceleration and maternal behavior (Ludwig & Pittman, 2003)—oxytocin has received attention due to its effect of reducing the activity of the hypothalamic-pituitary-adrenal (HPA) axis (Theodoridou *et al.* 2009; Modahl *et al.* 1998; Jansen *et al.* 2006) and reducing anxiety-related behaviors (Singer *et al.* 2008; Domes *et al.* 2010). Oxytocin neurons are activated by various stress stimuli and release oxytocin to attenuate the stress response (Takayanagi & Onaka. 2021). In our study, oxytocin levels tended to be higher among telecommuters than among office workers, suggesting that the security of staying in a familiar space stabilizes the mind and increases the amount of oxytocin that is secreted.

Cortisol is a steroid hormone secreted by the adrenal cortex and is a reliable biological indicator of the stress response of the HPA system, and stress increases cortisol levels in blood and saliva (Izawa *et al.* 2008). S-IgA is a type of antibody that prevents the growth of pathogens in the mucosa and is a major defense mechanism against mucosal infections of the oral and respiratory tract (Bosch *et al.* 2002). Chronic stress is associated with a decreased immune function (Cohen & Pollack. 2005; Mills *et al.* 2004) and chronic stress decreases s-IgA (Gallagher *et al.* 2008). Cortisol has a slower peak response, and both cortisol and s-IgA are thought to be indicators of long-term stress. In the present study, cortisol and s-IgA were not modulated in either group. Depending on the time and duration of the experiment, it may be important to evaluate these indices, and will be of interest to see if there are any changes with continued observation of this study population.

The present study was associated with several limitations. This was a preliminary single arm study that only included a relatively small number of Japanese subjects; thus, the findings and may be applicable only to certain ethnic groups. Previous studies on the serotonin transporter gene have shown that Japanese people tend to feel anxiety easily, and that a large proportion of genetic polymorphisms are associated with a tendency to avoid damaging behaviors by making various preparations in

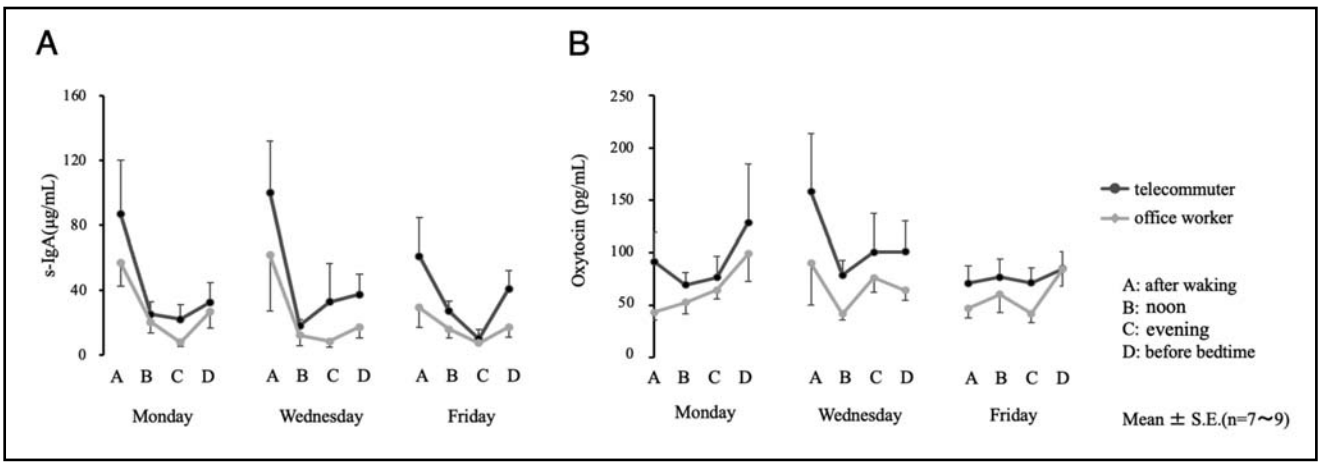

Fig. 3. Changes in salivary s-IgA levels (A) and salivary oxytocin levels (B)

advance (Murakami *et al.* 1999). In addition to racial differences, it is thought that people feel stress differently depending on their usual living environment (e.g., whether they have pets or houseplants) and the nature of their work. Further validation of the survey results would require the examination of a larger sample size after adjusting for these confounding factors.

In conclusion, the results suggest that telecommuters do not feel stress in relation to commuting to work, and they have fewer opportunities for human contact, which reduces their infection-related anxiety. On the other hand, the diurnal variation of melatonin was modulated in telecommuters, suggesting that the circadian rhythm was modulated by the change in life rhythm caused by being at home all day.

ACKNOWLEDGEMENTS

The authors would like to thank all of the participants in the present study.

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