

The Calming Effect of Stimuli Presentation on Infant Japanese Macaques (*Macaca fuscata*) under Stress Situation: A Preliminary Study

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ABSTRACT. In human newborns, presentation of sounds and odors under stress situations had a calming effect on behavioral and cortisol responses (KAWAKAMI et al., 1996, 1997). These calming effects were examined with 10-day- and 15-day-old Japanese macaques. In Study 1, white noise presentation (Experimental conditions) at the blood sampling was compared with no sound presentation (Control conditions) at the blood sampling. White noise presentation has a calming effect on coded behavioral responses. In Study 2, lavender scent presentation (Experimental conditions) at the blood sampling was compared with no odor presentation (Control conditions) at the blood sampling. Lavender presentation has a calming effect on cortisol responses in the marginal level. From the data of these studies, the salivary cortisol levels were related to the cortisol levels in plasma. Our results may suggest the different effects of sound and odor on infant Japanese macaques.

Key Words: Infant Japanese macaques; Stress; Cortisol.

INTRODUCTION

Stimulus presentations calm the stress of human newborn infants (KAWAKAMI et al., 1996, 1997). KAWAKAMI et al. (1996) presented white noise and heartbeat sounds during heelstick treatment for collecting blood, and found the significant calming effects on both coded behavioral responses such as facial expressions and crying, and cortisol responses. Next, KAWAKAMI et al. (1997) presented an artificial odor of milk and an artificial odor of lavender to human newborns during the heelstick treatment. Odor presentations had significant calming effects only on cortisol responses but not on coded behavioral responses. From these results, KAWAKAMI et al. (1996, 1997) proposed the attention hypothesis to explain the calming effects of the stimulus presentations on infant stress. Stimulus presentations shift attention of human newborns from stressful events to environmental stimuli. This hypothesis cannot explain the different results of modalities, but is of importance from the comparative developmental perspectives on the one hand. There are many studies concerning psychological stress such as social isolations on the adult, juvenile, and infant macaques (COE & HALL, 1996; MEYER & BOWMAN, 1972; ROWELL & HINDE, 1963; SACKETT et al., 1973; SHANNON et al., 1998; SMITH & FRENCH, 1997; YOUNG et al., 1973), but we have relatively few data concerning neonatal stress in nonhuman primates. The main purpose of this study is to examine the following questions: Do very early experiences of stress events have functionally similar effects on monkeys as in humans? And the second purpose of this study is, related to the first one, to think the next question: Are there some calming effects of various types of stimulus presentations also in neonatal monkeys such as sound (examined in Study 1) and odor (Study 2)?

Concerning our second purpose of the present study, comparative study of stress coping is

also of clinical importance on the other hand. Blood sampling is one of the stressful treatments for the laboratory primates irrespective of their ages (REINHARDT & REINHARDT, 2000). To reduce the stress for the blood sampling is one of the central problems for humane care and animal welfare of the nonhuman primates. For example, many researchers and technicians try to sample the blood very quickly to reduce the stress, and others successfully trained the monkeys to "cooperate with humans" for blood sampling using positive reinforcement (REINHARDT, 1991, 1996, 1997). If the stimulus presentations had calming effects on stress in infant monkeys, this would be another way for humane treatment of blood sampling.

In humans, salivary cortisol is frequently used for the assessment of the stress for newborns (FRANCIS et al., 1987; GUNNAR et al., 1989, 1992; SPANGLER, 1991; SPANGLER & SCHEUBECK, 1993; TAKAI-KAWAKAMI et al., 1995) and from 2-month-olds to 2-yr-olds (LEWIS & RAMSAY, 1995; LEWIS et al., 1993). These studies confirmed the stability and reliability of salivary cortisol as an index of responses to stress. There are also some studies investigating the salivary cortisol in nonhuman primates. BOYCE et al. (1995) showed that salivary cortisol measures could be used to express circadian activity in rhesus macaques (*Macaca mulatta*). FUCHS et al. (1997) claim that salivary cortisol is a non-invasive measure of hypothalamo-pituitary-adrenocortical (HPA) activity in squirrel monkeys (*Saimiri sciureus*). There are, however, no reports examining the relationship between salivary cortisol and stress in the newborn and/or infant primates. The third purpose of this study is to evaluate the usefulness of the salivary cortisol also in the infant macaques for the assessment of stress as in humans. When the salivary cortisol is easily obtained from infants and correspond reliably to the other invasive and/or non-invasive physiological measures, this measure should be a new non-invasive method of laboratory primate infants.

STUDY 1: THE EFFECT OF SOUND ON INFANT JAPANESE MACAQUES UNDER STRESS SITUATION

Extreme sound such as loud, unpredictable noise has negative effects on stress in humans and animals (BOWERS et al., 1998; DE-BOER et al., 1989; EVANS et al., 2001; OUIS, 2001). But adequate presentations of specific types of sound to humans such as soft-amplitude music have some positive effects on mood, anxiety, and cognitive performances (COCKERTON et al., 1997; STAUM & BROTONS, 2000). KAWAKAMI et al. (1996) presented the various kinds of sounds to 5-day-old human infants during the heelstick treatments and found stress-calming effects. In Study 1, the similar procedure to KAWAKAMI et al. (1996) was adopted to assess the calming effect of sound in macaque infants.

METHOD

Subjects

The final subjects were eight infant Japanese macaques (*Macaca fuscata*) born at the Primate Research Institute, Kyoto University.¹⁾ Seven of them were males and one female. Five of them were reared by their own mothers and three were reared by human caregivers. LEVINE and WIENER (1989) and SUOMI (1991) reported that separation of infant monkeys from their biological mothers produced an increase in levels of plasma cortisol. But there were no differences in levels of plasma cortisol between those reared by their own mothers and those reared by human caregivers [20.6 vs 24.0, $t(14)=0.47$, $p>.05$]. So they were combined in the following analyses.

The mean of the first experimental day was 12.5 days (range=5 – 21) and that of the second experimental day was 17.8 days (range=10 – 27) after birth. The mean body weight was 524.33g ($SD=101.75$) on the first experimental day and 537.33g ($SD=100.82$) on the second experimental day.²⁾ Care and use of the monkeys adhered to the 1986 version of the “*Guide for the Care and Use of Laboratory Primates*” of the Primate Research Institute, Kyoto University.

Procedure

White noise was generated by sound-editing software running on a computer (Apple Macintosh), and was presented by a cassette deck (SONY, CFS-DW30). According to STEBBINS (1970), the adult macaques appear to discriminate small differences in frequency with an acuity only slightly less than that of humans. But there were no reports on developmental changes in auditory perception of macaques. So we infer that infant Japanese macaques have almost the same abilities as human newborns. The sound pressure level, 85 dB (same as in human experiments) at the subject’s ear, was measured by a sound pressure meter (Rion, NA-80) and condenser microphone (Rion, UC-30). Sounds were presented from beginning to end of the first blood sampling (see later).

All experiments in this study were performed at the Primate Research Institute, Kyoto University. At this institution, infants, reared by their own mothers, lived in individual stainless steel cages (0.87m W × 0.8m D × 0.87m H). Infants, reared by human caregivers, were held by caregivers more than 5 hr and were given milk every 6 hr in the day time, and they were paired and lived in individual stainless steel cages for the rest of the day time and night time. The range of the temperature of the rooms was between 10° to 25°C. The day/night cycle of the rooms was artificially illuminated from 06:00 to 18:00.

Unlike in KAWAKAMI et al. (1996), we only used white noise as stimulus and tested the subjects using within-subjects designs. Each subject was tested twice with one of the experimental and control conditions. We collected the blood samples twice under the same conditions to check the relationship between plasma and salivary cortisol.

All procedures were performed from 10:00 to 13:00. At the experiment, each subject was brought to an experimental room to shut out the effect of other monkeys and to keep the same experimental conditions. “The first saliva sampling” was collected from each subject before “the first blood sampling.” This first blood sampling was treated as stress. All blood samplings were performed by one veterinarian. The longest duration of the blood sampling was 95 sec. After the first blood sampling, subjects stayed on the experimental table supported by the experimenters. “A post-blood-sampling (the second) saliva sample” was performed 20 min after the beginning of the first blood sampling. This timing was based on results of LEWIS and THOMAS (1990) and LEWIS et al. (1993) on human infants. After the second saliva sampling, “the second blood sampling” was performed. During the whole experimental procedure, the facial and vocal state of the subject was recorded by video for later behavioral scaling. Only one condition was presented on each examination day. In the experimental condition white noise was presented, and in the control condition no sound was presented. The order of the two conditions was counterbalanced.

The videotaped segments of “the first blood sampling” procedure were coded for subjects’ facial and vocal expression during 5-sec intervals. LEWIS et al. (1993) used a 4-point scale (from full distress to no distress) for human infants’ facial expression, but this is impossible with mon-

1) We could not assess one infant’s cortisol level in plasma. It was eliminated from the subjects. 2) We could not record the body weight data of two subjects.

keys. So a 2-point scale was adapted: 1 (distress) and 0 (no distress). Vocal expression was also coded on a 2-point scale: 1 (cry) and 0 (no sound). Facial and vocal measures had a high concordance, so they were combined into a scale ranging from 0 to 2. All data were coded by two coders independently. The percentage of intercoder agreement was 96.6%.

The saliva sample was collected by dental cotton roll. Saliva, absorbed by the cotton, was placed into test tubes. Blood samples were drawn with syringes containing 1% sodium heparin. Saliva samples and blood samples were immediately centrifuged at 1000 g for 20 min at 4°C. The saliva and plasma samples were stored at -30°C. Salivary and plasma cortisol concentrations were determined by EIA (enzymeimmuno assay). All the cortisol assays done in a single batch. Intra- and inter-assay coefficients of variation were between 15.2 and 17.8% in low dose, and between 7.4 to 8.7% in high dose, respectively. Reagents including cortisol (hydrocortisone) for standard, peroxidase labeled cortisol, and O-phenilendiamine were purchased from Sigma (Tokyo, Japan). The antibody to cortisol was obtained from Cosmobio (Tokyo, Japan). Microplates were obtained from Gleiner (Tokyo, Japan).

RESULTS

Behavioral Response

As the duration of the first blood sampling was different among subjects [mean=10.94 (5-sec intervals), range=3 - 19], the means of coded behavioral responses per 5-sec intervals were compared. The mean of coded behavioral responses by Control (CONT) conditions was .50 ($SE=.12$) and that of Experimental (EXP) conditions was .37 ($SE=.13$). A one-way ANOVA with a repeated measures factor for means yielded no significant effect, $F(1,7) = 2.55, p=.16$. Figure 1 shows the data by each subject. The dashed line shows the subject reared by human caregivers.

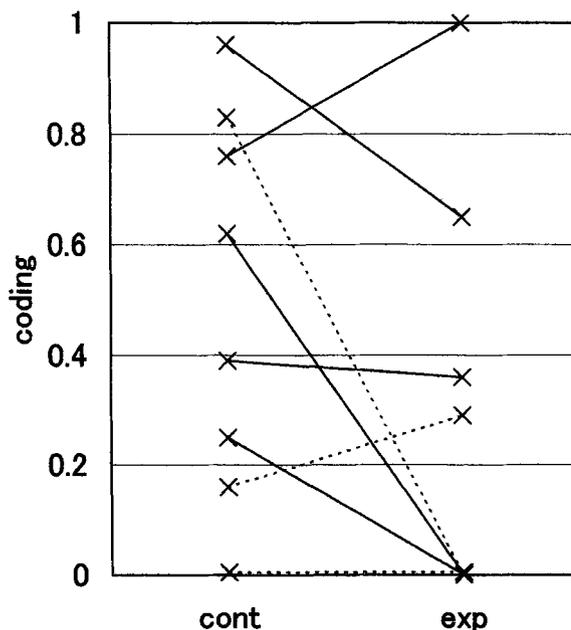


Fig. 1. Coded behavioral responses by each subject (Study 1).

Table 1. The first blood sampling and the second blood sampling cortisol levels in micrograms/deciliter in the two conditions.

	CONT	EXP
First blood	22.25 (5.79)	21.50 (3.95)
Second blood	30.88 (8.61)	31.25 (7.80)

Standard errors are given in parentheses.

To explore the effect on behavioral responses further, the proportions of no distress and no sound in whole 5-sec intervals were compared between conditions by chi-square. In EXP conditions the proportions of no distress and no sound in whole 5-sec intervals were significantly larger than those of CONT conditions [72.37 vs 51.52 , $\chi^2(1)=15.66$, $p<.001$].

Cortisol Response

The first blood sampling (referred to as Cortisol A) and the second blood sampling (Cortisol B) cortisol levels in plasma are shown in Table 1. A two-way ANOVA with a repeated-measures factor for conditions and a repeated-measures factor for cortisol (A and B) was performed. This ANOVA yielded a marginal effect of cortisol sample, $F(1,7)=4.29$, $p=.077$. There was a little increase in cortisol level following the first blood sampling. There was no significant main effect of conditions and cortisol sample X conditions interaction. Figure 2 shows the data by each subject. The horizontal axis shows delta cortisol (Cortisol B minus Cortisol A).

The data of salivary cortisol will be analyzed in Study 2.

DISCUSSION

In behavioral responses there was a significant effect of white noise presentation in some

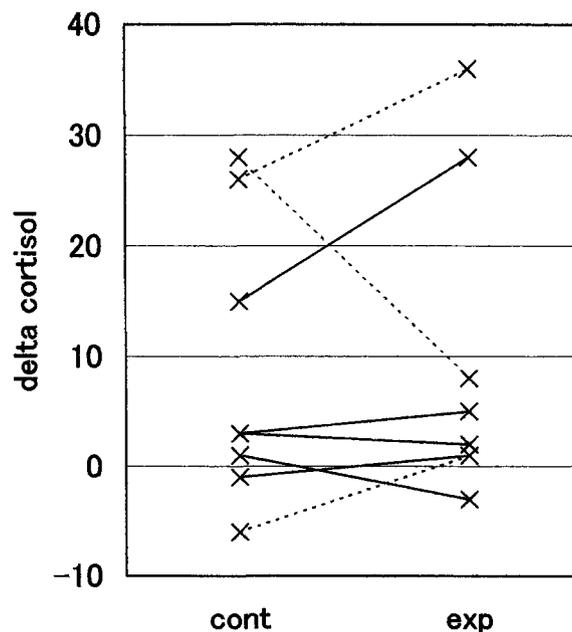


Fig. 2. Delta cortisol (micrograms/deciliter) by each subject (Study 1).

aspects. But in cortisol responses, there was no strong effect of white noise presentation. As Figures 1 and 2 show, the data of one subject were atypical and affected the present nonsignificant results. In contrast to the present study, the effect of sounds presentation was found on human newborns under stress on both behavioral and cortisol responses (KAWAKAMI et al., 1996). In their study, an 8-point scale was used for behavioral responses, but a 2-point scale here. In human study, the duration of the blood sampling was almost 5 min, but very short here. And the small number of cases might cause these results. It may be relatively large variations of responses in Japanese macaques, comparing with those in humans in this kind of study. These procedural differences might be responsible to the present results.

The whole procedure needed about one hour per subject in the present experiment. But "the stress of capture" (cf. BOYCE et al., 1995) should be very little here. It needed only a short time for the blood sampling as mentioned before. So only the blood sampling might be treated as the stressor here.

STUDY 2: THE EFFECT OF ODOR ON INFANT JAPANESE MACAQUES UNDER STRESS SITUATION

In humans, some types of odor (such as lavender) have positive effects on affection (LUDVIGSON & ROTTMAN, 1989) although the others such as artificial chemical odors cause stress effects (ASMUS & BELL, 1999; STEINHEIDER & WINNEKE, 1993). KAWAKAMI et al. (1997) also found that the lavender and milk odor had stress-calming effect in human neonates. In Study 2, odor stimuli instead of sound were presented during the same procedures as in Study 1.

In infant monkeys, odor perception has an important role in their lives [squirrel monkeys: KAPLAN & RUSSELL, 1974; KAPLAN et al., 1976; long-tailed macaques (*Macaca fascicularis*): NEGAYAMA & HONJO, 1986]. In adults, this is also true [saddle-back tamarins (*Saguinus fuscicollis*): EPPLE & NIBLICK, 1997; capuchins (*Cebus apella*): UENO, 1994a, b, c]. But to date, little information on the ontogenetic development of the scent glands is available (EPPLE et al., 1993). Furthermore, there are no reports concerning effects of odor on stress in nonhuman primates.

METHOD

Subjects

Seven infant Japanese macaques born at the Primate Research Institute, Kyoto University. Four of them were male and three females. There were no sex differences in the results. Five of them were reared by their own mothers and two were reared by human caregivers. The mean of the first experimental day was 9.7 days (range=7 – 12) and that of the second experimental day was 14.0 days (range=11 – 17) after the birth. The mean body weight of the first experimental day was 576.57 g ($SD=76.27$) and that of the second experimental day was 598.57 g ($SD=79.15$).

Procedure

The lavender odor was used as the stimulus in this study, because many studies used it and found the calming effects of it on human adults (e.g. DIEGO et al., 1998; ITAI et al., 2000; YAGYU, 1994). Linalyl acetate (L.G.) served as the lavender odor. It was diluted in odorless triethyl citrate (TEC) solvent to 10% concentration. The odor and solvent were supplied from

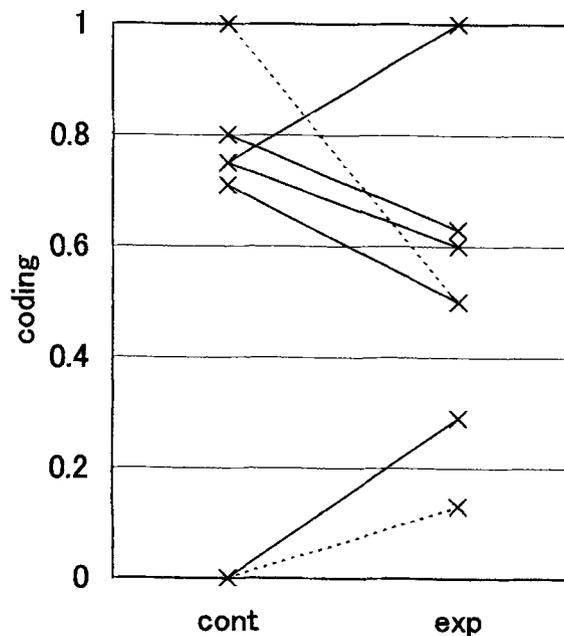


Fig. 3. Coded behavioral responses by each subject (Study 2).

Takasago International Corporation (Kanagawa, Japan). To present the odor stimulus, a smelling blotter of 1.5 cm depth from the tip was put in a bottle filled with the odor stimulus and then placed in front of the nose (2 – 3 cm from the nasal cavity) during the first blood sampling. Except for this stimulus presentation, the whole procedure was the same as in Study 1.

RESULTS

Behavioral Response

Intercoder agreement was 92.8%. The mean of coded behavioral responses by Control conditions was .57 ($SE = .15$) and that of Experimental conditions was .52 ($SE = .11$). A one-way ANOVA with a repeated-measures factor for means yielded no significant differences among conditions [$F(1,6) = .23, p = .65$]. Figure 3 shows the data by each subject. The dashed line shows the subject reared by human caregivers.

Cortisol Response

The first blood sampling (Cortisol A) and the second blood sampling (Cortisol B) cortisol levels in plasma are shown in Table 2. A two-way ANOVA with a repeated-measures factor for conditions and a repeated-measures factor for cortisol (A and B) was performed. This ANOVA yielded a significant effect of cortisol sample, $F(1,6) = 31.92, p < .001$. There was a reliable increase in cortisol level following the blood sampling. The condition effect was marginal levels of significance, $F(1,6) = 5.04, p = .066$. The CONT conditions had a slightly higher cortisol levels than the EXP conditions. The cortisol sample X conditions interaction was not significant. Figure 4 shows the data by each subject.

Table 2. The first blood sampling and the second blood sampling cortisol levels in micrograms/deciliter in the two conditions.

	CONT	EXP
First blood	18.71 (3.03)	15.00 (2.91)
Second blood	30.43 (6.46)	22.57 (1.96)

Standard errors are given in parentheses.

Relations Between Plasma and Salivary Cortisol Levels

To examine the reliability of the salivary cortisol levels as a stress measure, relations of plasma and salivary cortisol levels of all available data (Studies 1 and 2) were analyzed. All comparable combinations of cortisol A in saliva and plasma, and cortisol B in saliva and plasma were 36. Figure 5 shows the results by plasma cortisol as the horizontal axis and salivary cortisol as the vertical axis. Pearson's correlation was significant, $r = .38$, $p < .05$.

The mean of plasma cortisol levels ($n = 36$) was 23.14 microgram/deciliter ($SE = 2.36$) and that of saliva was 4.39 microgram/deciliter ($SE = .42$).

DISCUSSION

In behavioral responses there was no significant effect of lavender presentation, but a slight effect was found in cortisol responses. This small effect might be from the small numbers of subjects.

From the relations between plasma and salivary cortisol levels, the salivary cortisol is a reliable index of stress in infant Japanese macaques. But it is necessary to get enough saliva to sample it. Researchers often use oral stimulants to collect enough amount of saliva in human

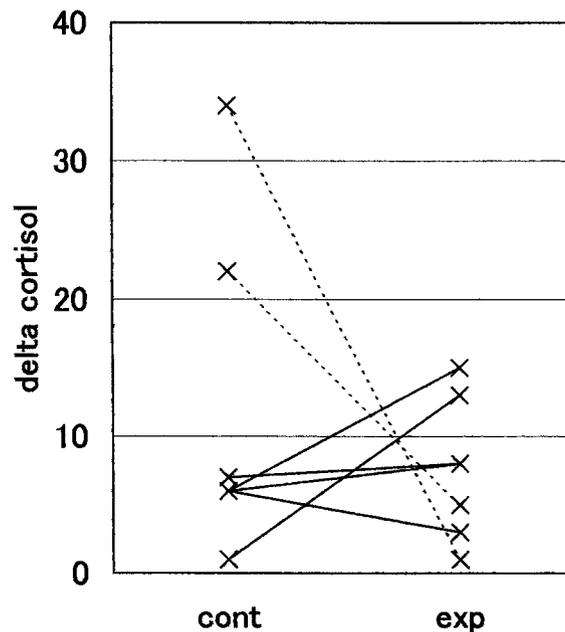


Fig. 4. Delta cortisol (micrograms/deciliter) by each subject (Study 2).

subjects (e.g. LEWIS et al., 1993; SCHWARTZ et al., 1998). In the present experiment, however, we did not use unsweetened lemon crystals, because the oral stimulants sometimes affect salivary cortisol in humans. SCHWARTZ et al. (1998) found that when added directly to saliva samples, oral stimulants artificially inflated estimated cortisol concentrations in humans. We should examine the artificial effects of oral stimulants on salivary cortisol in infant macaques. If this artifact can be reliably controlled, it would be recommended to use unsweetened lemon crystals for infant monkeys to increase the amount of saliva sample.

In humans, concentrations in saliva are about one sixth of that in plasma (KAWAKAMI et al., 1996). In the present studies, the data under both non-stress and stress conditions were used to analyze relations between salivary and plasma cortisol, and the mean of salivary cortisol levels was one sixth of that in plasma. This ratio is comparable to our previous study with human neonates (KAWAKAMI et al., 1996). In adult rhesus macaques, however, concentrations in saliva are about one tenth of that in plasma under non-stress conditions (BOYCE et al., 1995). There might be several reasons to yield this difference; age difference, experimental conditions, assay procedures, and species difference. At present, however, it is unclear what factors actually affected this difference between the previous and the present studies with macaques. It should be further examined the relationships between the salivary cortisol and the cortisol measures from the other samples such as, urine and feces.

GENERAL DISCUSSION

The present experiments examined the stress-calming effects of the presentation of various types of stimuli such as sound and odor on the neonatal Japanese macaques during the blood sampling. Our main purpose was threefold. First is the examination of attentional hypothesis from the comparative perspective. The second is the enrichment or animal-welfare implication for reducing stress during the blood sampling, which is very common activity in laboratory primate facility. And the third is the assessment of the utility of salivary cortisol as a noninvasive measure for some physiological assay.

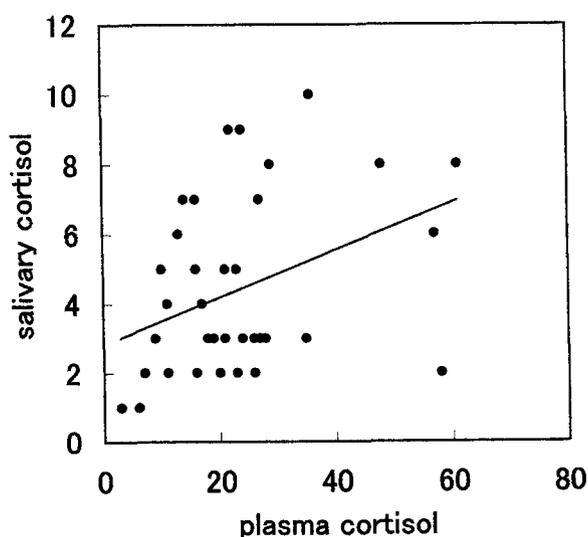


Fig. 5. Relations between plasma and salivary cortisol levels (micrograms/deciliter).

Table 3. The summary of all results: comparisons between infant Japanese macaques and human infants.

	Infant Japanese macaques	Human infants
White noise		
Cortisol	–	***
Behavior	**	***
Lavender		
Cortisol	*	***
Behavior	–	–

*** Significant effect; ** significant effect partially; * conventional effect; – : no effect.

In human newborns, presentation of sounds and odors under a stress situation had a calming effect (KAWAKAMI et al., 1996, 1997). But in Study 1, presentation of white noise under the same situation had no effect on cortisol responses of infant Japanese macaques, but had a positive effect on behavioral responses. And in Study 2, presentation of odor of lavender had a slight effect on cortisol responses. Table 3 shows the summary of results of all experiments on infant macaques and human infants of our previous studies. In the present experiment, we tested the neonates around 10-day-old. One week of postnatal visual maturation in the macaque appears to represent one month in the human (GUNDERSON & SACKETT, 1984). So 10-day-old macaques are almost the same as 40-day-old humans. On the other hand, mean age of human neonates in KAWAKAMI et al.'s studies was 5-day-old. This difference might have some different effects between human and monkey neonates. The effect of stimuli presentation in studies of KAWAKAMI et al. (1996, 1997) should be retested on 40-day-old humans for further comparisons with the results of these studies. Furthermore, testing with macaques of different ages such as adults will be conducted from the developmental perspective.

Our results may suggest the different effects of sound and odor on the “attention” of infant Japanese macaques. This possibility can be addressed under some other situations. For example, does environmental sound or odor have some effect on stress in adult monkeys? If so, are there any differences in effect between sound and odor? The introduction of controlled environmental sound and odor also will be important from the perspective of animal welfare, our second purpose (cf. MILLIGAN et al., 1993).

The third purpose of this study was to examine the salivary cortisol data in Japanese macaques. As shown in Figure 5, we found reliable correlations between cortisol levels in saliva and plasma. Also the ratio of cortisol levels between saliva and plasma was similar to human neonates. Taken together, salivary cortisol can be used as indices in laboratory studies if we can have a sufficient amount of saliva. We need to explore further technical improvements to increase the amount of saliva samples such as use of unsweetened lemon crystals.

In sum, our results have implications on various aspects such as comparative development, stress reactions, medical primatology, and animal welfare. In the future, we should further examine the effect of stimulus presentations on stress responses in nonhuman primates to contribute the development of these areas of research.

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