Journal of the American Association for Laboratory Animal Science
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Vol 52, No 2
March 2013
Pages 157–164

Effects of Acute Psychosocial Stress in a Nonhuman Primate Model of Allergic Asthma

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Current husbandry and care guidelines for laboratory animals recommend social housing for nonhuman primates and all other social species. However, not all individuals of a social species are compatible, which can lead to psychosocial stress on certain members. Because stress affects immune responses, we undertook the present study to determine whether psychosocial stress associated with changes in the group housing of nonhuman primates affected allergic responses in a nonhuman primate model of allergic asthma. Historic records from 35 cynomolgus macaques (*Macaca fascicularis*) sensitive to house dust mites (HDM) and enrolled in asthma studies from 2007 to 2011 were reviewed for variations in response to aerosolized HDM that could not be explained by clinical or experimental interventions. We then compared these variations with husbandry and clinical records to determine whether the unexplained variations in responses were associated with events known to induce psychosocial stress in this species, including restructuring of social groups, temporary isolation of group members, and changes in cage or room configurations. Adult macaques in stable social groups exhibited little variation in responses to aerosolized antigen. Changes in group membership (conspecifics), cage configurations, and temporary isolation of a group member were associated with decreased responses to HDM. This attenuation lasted 2 to 3 mo on average, although some macaques showed prolonged responses. No evidence for a stress-induced increase in allergic responses was noted. These results demonstrate that acute stress in HDM-sensitive cynomolgus macaques diminishes the physiologic response to inhaled allergen.

Abbreviations: AU, arbitrary units; HDM, house dust mite; PC_{HDM}, provocative concentration of HDM antigen.

Psychosocial stress affects the functions of multiple organ systems through integrated humoral and neural mechanisms and has been implicated in the pathogenesis of cardiac and respiratory diseases, including asthma.[10] Unraveling the mechanisms that underlie stress responses is complicated by diversity in stimuli (that is, stressors), variation in how different subjects perceive the stimuli, length of time for which the stimulus is perceived as stressful, and when physiologic measurements to assess the effect of stressors are recorded. The complexity of human society and living conditions make it difficult to conduct and implement well-controlled studies of the effect of chronic stress on disease processes. In contrast, definitive studies have been conducted in animals, with many studies in nonhuman primates because of their similarity to humans in regard to living long lives in socially rich environments.

Psychosocial stress has the potential to affect asthma at multiple levels, directly inducing exacerbations in some patients and increasing the incidence and severity of asthmatic responses to environmental triggers for extended periods of time.[22] At another level, there is evidence that asthma itself induces psychologic stress, thereby establishing a positive feedback augmentation of the disease.[8] Whether the response to stress is due to direct activation of immune and airway effectors or is secondary to cognition or a cognitive process that exerts control over those effectors is unclear. In addition, the integrated response to periodic acute stress in the context of ongoing chronic stressors is not well defined; and the relative roles that cognition, sensation, hormones, and autonomic control play in airway inflammation and function under these conditions are unknown.

Received: 26 Jul 2012. Revision requested: 28 Aug 2012. Accepted: 03 Oct 2012.
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Studies conducted in both animals and humans over 3 decades reveal strong associations between psychosocial stress and immune function, to the extent that alteration in immune function is considered to be a defining characteristic of a stress response.[10] Longitudinal studies of nonhuman primates in captivity have revealed both short-term and lifelong changes in immune function after a stressful event such as rehousing, destabilization of dominance hierarchy, or separation from the social group. In these animals, acute stress elevates cortisol levels, decreases numbers of circulating $CD4^+$ and $CD8^+$ cells, and reduces lymphocytic responses to mitogens and antigens for as long as 2 mo.[9] Prolonged separation early in life can lead to decreased disease resistance and a shorter lifespan.[16,17] Whether these changes in immune function manifest as altered allergic responses and expression of asthma symptoms in research subjects has not been reported. Previous literature has examined the role of psychosocial factors in the development of asthma in rhesus macaques.[7] Others have documented that SIV-infected rhesus macaques die sooner when faced with psychosocial experiences that likely produce stress.[6]

The present study was undertaken to determine whether psychosocial stress in nonhuman primates is associated with altered respiratory responses to aeroallergen. From 2007 to 2011, 35 cynomolgus macaques were housed and maintained with established sensitivity to house dust mite (HDM). During this period, macaques were challenged with aerosolized HDM extract according to a set schedule. The provocative concentration of HDM antigen (PC_{HDM}) and acute changes in lung resistance, dynamic compliance, and pO_2 were recorded and archived. For this study, historic records were reviewed for alterations in pulmonary responses to aeroallergen. These records were independent of clinical and experimental interventions and were preceded by restructuring of social groups, temporary isolation

of group members, or changes in cage or room configurations; all of these events are psychosocial stressors of macaques.

Materials and Methods

Cynomolgus macaques (*Macaca fascicularis*; *n* = 35) born between 1998 and 2006 were obtained and maintained at East Carolina University. Twice annually, the colony was monitored for simian retroviruses, simian T-cell leukemia virus, herpes B virus, and SIV via multiplexed fluorometric immunoassays; in addition, macaques were tuberculin-tested intradermally. Annually, the colony underwent fecal analysis for parasites and fecal culture for *Shigella*, *Campylobacter*, and *Salmonella* spp. The macaques had ad libitum access to water via an automated watering device , were fed chow twice daily (LabDiet Monkey Diet 5038, Purina Laboratory, St Louis, MO), and were supplemented daily with fruits and vegetables. The light cycle was maintained on a 12:12-h light:dark cycle. Macaques typically were housed indoors in same-sex groups of 2 to 6 macaques in stainless steel caging that included gang caging and vertical tunnels connecting upper and lower batteries to provide vertical mobility and voluntary visual and physical separation from cagemates. In 3 cases, macaques were singly housed due to extreme aggression toward or from other animals. In these cases, caging included at least 4 ft of vertical height and 8 ft^2 of floor space and permitted visual contact with other animals within the room when mutually desired. Temporary separation of macaques for experimental monitoring or clinical interventions was accomplished by using screens that maintained visual and tactile connection whenever feasible. The fresh-air supply to rooms housing macaques was filtered at MERV 8 (< 3 to 10 µm particle diameter) to minimize exposure to environmental allergens. The macaques were assigned to IACUC-approved protocols and were maintained consistent with the USDA Animal Welfare Act and regulations and the *Guide for the Care and Use of Laboratory Animals*.[1,2,19] The animal care and use program at East Carolina University is USDA-registered, maintains a Public Health Services Assurance, and is fully accredited by AAALAC.

Allergic sensitization and assessment of allergic sensitivity. The sensitization of the macaques, development of airway responses, and changes in gene expression over time have been described previously.[3,20,21] A systemic immune response was induced by intraperitoneal or subcutaneous injection of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extract. After systemic sensitization, macaques were challenged with nebulized HDM every 4 to 8 wk to induce and maintain pulmonary sensitivity.

Changes in pulmonary function associated with allergen challenge were evaluated as previously reported.[20,21] Subjects were anesthetized with Telazol (2.5 mg/kg IM; Fort Dodge Animal Health, Overland Park, KS) and propofol (10 to 15 mg/kg IV hourly). Lung dynamic compliance and resistance were measured by standard computer analysis of the flow and pressure signals. Baseline parameters were recorded, saline was delivered via ultrasonic nebulization for 4 min, and then increasing concentrations of HDM allergen (1, 10, 100, 500, and 2500 arbitrary units [AU] per milliliter) were delivered at 5-min intervals until a 100% increase in lung resistance or 40% decrease in dynamic compliance was achieved. SpO_2, blood pressure, and heart rate were monitored continuously. Supplemental O_2 was administered when SpO_2 fell below 70%. Provocation was discontinued when SpO_2, blood pressure, or heart rate was not maintained.

Serum HDM-specific IgE levels were measured by using a commercially available kit as previously reported.[3,21] HDM-specific IgE levels in serum were reported as percentages of the levels in historic allergic and naïve control serum samples.

Data analysis. Historic data archived in a database (Access, Microsoft, Redmond, WA) were reviewed for the maximal concentrations of HDM aerosol delivered to macaques in the colony and the resulting changes in lung resistance and dynamic compliance and SpO_2 during the 15-min after provocation. The data were plotted against time; regression line and 95% confidence intervals were plotted, and deviations in responses were noted. Dates associated with changes in responses were used as queries against experimental, clinical, and husbandry records to identify events coincident with the changes in responsiveness. Data before and after specific events were compared by using the Student paired *t* test or ANOVA with the Tukey posthoc test as appropriate. A *P* value of less than 0.05 was considered to be significant. Data are reported as either representative tracings or mean ± SE.

Results

Intrinsic variability in sensitivity to HDM was assessed by plotting the mean periodic responses to HDM in 35 allergic macaques from October 2009 through March 2011, a time period representing minimal clinical and experimental intervention. Table 1 presents the average physiologic and inflammatory characteristics of these macaques (allergic group) relative to HDM-insensitive animals in the colony (nonallergic group). There was no statistically significant change in provocative concentrations of HDM aerosol across the time period, although it trended upward (Figure 1 A). Likewise, changes in lung resistance and dynamic compliance were not statistically significant, although they tended to decrease over time. Of note, the target changes of at least 100% in lung resistance and 50% in dynamic compliance were achieved throughout the period (Figures 1 B and C). Therefore, for the entire group of allergic macaques, responsiveness to HDM tended to decrease gradually over the 1.5-y period.

In November 2008, 7 adult macaques that were housed in 3 groups within the same room were rehoused such that battery housing containing a group of 4 female macaques and that housing a single male were attached to a common gang cage. The female macaques were given use of the cage in the evenings and at night, and the male macaque had use of the gang cage during the day. A mixed-sex pair shared the same room and had visual contact with the gang cage. Retrospective analysis of data collected before and after reconfiguring the room was performed to identify changes in allergic responses.

The concentration of HDM required to induce a 100% increase in lung resistance or 50% decrease in dynamic compliance was determined 11 times from September 2008 through January 2010 (Figure 2). The HDM sensitivities at the beginning and end of the observation period were nearly identical. However, PC_{HDM} became variable for 5 mo after the rehousing event. PC_{HDM} measured in January 2009 had increased in 3 of the 7 macaques, leading to an increase in the overall average PC_{HDM} within the room (Figure 2 A and B). Note that an increase in PC_{HDM} denotes a decrease in allergic sensitivity. The change in PC_{HDM} could not be explained by inadvertent overstimulation, because changes in lung resistance and dynamic compliance were not elevated (Figure 2 C and D). Transient changes in PC_{HDM} occurred in March and May 2010, but in each case, the deviation was caused by a single animal. By June 2010, PC_{HDM} had stabilized at the level observed before reconfiguration of the room. In 2 different social groups, we noted changes in allergic sensitivity after the composition of the groups was altered. In October 2009, a group

Table 1. Historic physiologic and inflammatory characteristics of the macaque colony

	Maximal Early Asthmatic Response					Cells from brochoalveolar lavage (% of total cell count)		
	PC_{HDM} (AU/mL)	ΔR_{Lung} (%)	ΔC_{dyn} (%)	SpO_2 (%)	HDM IgE (U/mL)	Lymphocytes	Eosinophils	Neutrophils
Allergic (n = 35)	419.37 ± 80.23	101.08 ± 15.33	−45.17 ± 2.23	79.59 ± 0.89	6.33 ± 0.54	2.41 ± 0.18	13.68 ± 1.28	4.67 ± 0.54
Nonallergic (n = 25)	1976.77 ± 92.90	16.33 ± 5.09	−13.85 ± 3.30	87.71 ± 1.00	2.49 ± 0.51	2.66 ± 0.52	2.99 ± 0.58	4.94 ± 2.06

PC_{HDM}, provocative concentration of HDM; $\%\Delta R_{Lung}$, change in lung resistance as a percentage of baseline; $\%\Delta C_{dyn}$, change in dynamic compliance as a percentage of baseline; SpO_2, minimum arterial O_2 saturation measured by pulse oximetry after HDM provocation; HDM IgE, serum concentration of HDM-specific IgE.

For macaques in the allergic group, PC_{HDM} refers to the concentration that elicited the target changes in R_{Lung} and C_{dyn}. For nonallergic macaques, PC_{HDM} is the maximal HDM concentration delivered.

of 7 juvenile males was divided to decrease the overall size of the group and address compatibility issues. A subordinate animal was removed from the group and rehoused with another subordinate animal from a different group within the same room. The 2 macaques were moved to a new cage in the same room. Two dominant macaques from the original group and one of the subordinate animals exhibited increases in PC_{HDM} (that is, decreased allergic sensitivity) after reconfiguration of the groups (Figure 3). In August 2010, 1 of 3 adult female macaques in a stable group died; the remaining 2 macaques showed increases in PC_{HDM} (Figure 3). Tracings from a representative macaque in the juvenile male group and the stable female group are shown in Figure 3 A. Prior to intentional reconfiguration of the male group, the macaque in Figure 3 A had been tested for allergic sensitivity 7 times, and for 5 of the 7 challenges, he responded to a HDM at a level of 100 AU/mL. After intentional reconfiguration of the group, this macaque consistently responded to 500 AU/mL. Prior to the death of her cagemate, the other macaque shown in Figure 3 A was highly sensitive to HDM, with a PC_{HDM} of 10 AU /mL inducing 100% to 300% increases in lung resistance and 40% decreases in dynamic compliance. After the death of her cagemate, the macaque required a higher concentration of allergen, 100 AU/mL, to induce the target changes in lung resistance and dynamic compliance. Aggregate data for all 5 HDM-sensitive macaques involved in these incidences are shown in Figure 3 B through E. All 5 macaques received higher doses of HDM aerosol after the social changes (Figure 3 B), yet the change in lung resistance decreased in 4 of the 5 macaques (Figure 3 C). A smaller change in lung resistance in response to a higher concentration of HDM represents a diminution in the sensitivity or responsiveness of the macaques to the antigen. Serum HDM-specific IgE levels had been measured before and after the group changes, and no consistent changes were noted (Figure 3 E). Therefore, social changes in these 2 groups led to decreased allergic responses that could not be explained by a decrease in serum IgE. These data indicate that changes in the composition of groups can affect allergic sensitivity of some animals, including the socially dominant animals.

In 2008 and 2009, increases in PC_{HDM} were noted in 11 macaques from diverse groups and rooms. Examination of the animals' records revealed that all of the animals had been enrolled in a telemetry study. The study was minimally invasive and simply tested whether inductance plethysmography could be used to detect nocturnal disturbances in respiration after daytime exposure to allergen.[23] Inductance plethysmography is a technique in which respiratory activity is remotely monitored in conscious, unrestrained subjects. The protocol involved anesthetizing the macaques, fitting them with telemetry jackets containing motion detectors, exposing the macaques to HDM aerosol, allowing the macaques to regain consciousness, and then monitoring respiratory activity for 24 h During the 24-h monitoring, the animals were separated from their social groups by a screen that allowed visual—but not tactile—contact. After 24 h, the jackets were removed and the macaques were returned to their social groups. Figure 4 A comprises representative tracings from 3 animals in the same social group. Macaque 6C38 exhibited stable PC_{HDM} prior to the study but increased PC_{HDM} after the telemetry session. Macaque 6C160 also exhibited a transient change in PC_{HDM} after the telemetry sessions involving his cagemates even though this animal itself never wore a jacket or was separated from the group. Macaque 6C160 typically interacts extensively with macaque 6C38 and frequently becomes distraught when they are separated. In contrast to these 2 macaque, a third cagemate, 6C32, who has a very low level of affiliation with other group members, demonstrated no change in PC_{HDM} with regard to HDM challenge and social instability.

For the 11 macaques that exhibited changes in PC_{HDM} after telemetry sessions in this timeframe, PC_{HDM} on the day of the study and at 6 to 8 wk prior to the study were similar (Figure 4 B). During the HDM challenge conducted 6 to 8 wk after the telemetry session, PC_{HDM} was significantly ($P < 0.05$) increased. Lung resistance and dynamic compliance were more variable 6 to 8 wk after the telemetry session than before it (Figure 4 C and D), but the changes fail to account for the one-log increase in PC_{HDM}.

Discussion

This analysis of allergic responses in 35 HDM sensitive cynomolgus macaques over a 4-y period revealed numerous occasions when higher than the usual concentration of aerosolized HDM antigen was delivered to specific animals to induce target changes in lung resistance and dynamic compliance. The increases in PC_{HDM} were associated with discrete events that are known to induce psychosocial stress in macaques, including changes in the physical environment, isolation of individuals, loss of group members, and restructuring of social groups. The responses to the events were observed independently in multiple macaques from different groups but were not manifested by all members of the group, indicating that a systematic error is unlikely to account for the observations. Previous reports in other nonhuman primates have documented that social and housing conditions affect the progression of viral disease.[4] Our observations are consistent with findings in nonhuman primates and rodents regarding acute stress, as compared

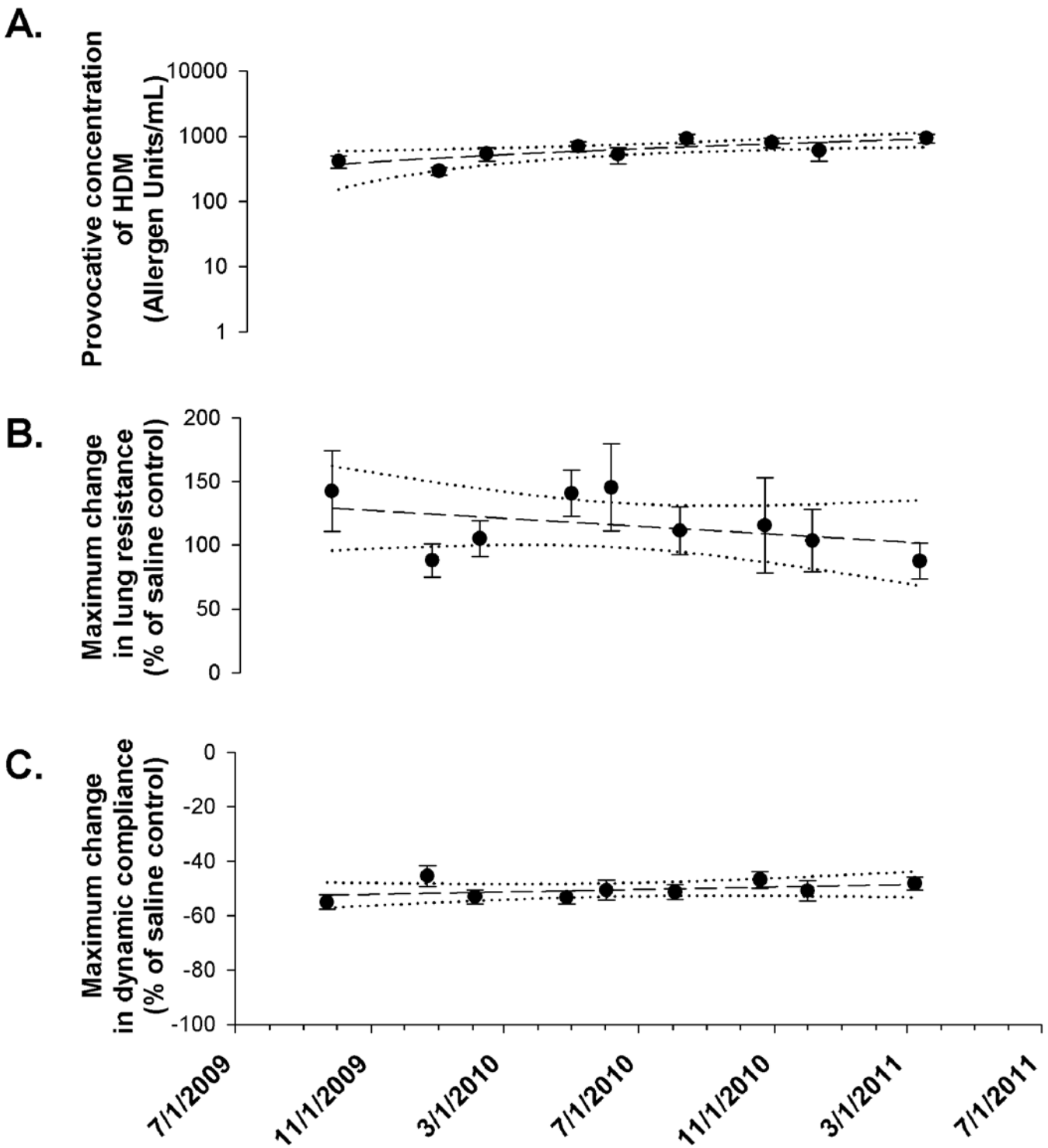

Figure 1. Longitudinal responses of all allergic animals within the colony. Periodically, 35 animals were challenged with aerosolized HDM. Data collected over a 1- to 2-wk period around the dates shown were averaged. The (A) provocative concentrations of HDM and maximal induced changes in (B) lung resistance and (C) dynamic compliance are shown as mean ± SEM. The regression line (dashed line) and 95% confidence intervals (dotted lines) for the data collected during these dates are shown.

with chronic stress, which augments allergen-induced airway inflammation, airway hyperresponsiveness, and asthma exacerbation.[22] These data demonstrate that allergic responses in group-housed animals are relatively stable in the absence of changes in the physical and social environments. However, change in the physical environment can transiently decrease allergic responsiveness in some animals.

Specific responses to acute stress are dependent on many factors, including the species, age of the animals, stressor, and timing of the observations; but, in general, animals from rodents to humans respond to acute social stress with stimulation of the hypothalamic–pituitary axis and transient elevation of corticosteroids, which can lead to reduction in circulating lymphocytes, decreased mitogen-induced lymphocyte proliferation, and decreased cytotoxic lymphocyte responses.[9,22]

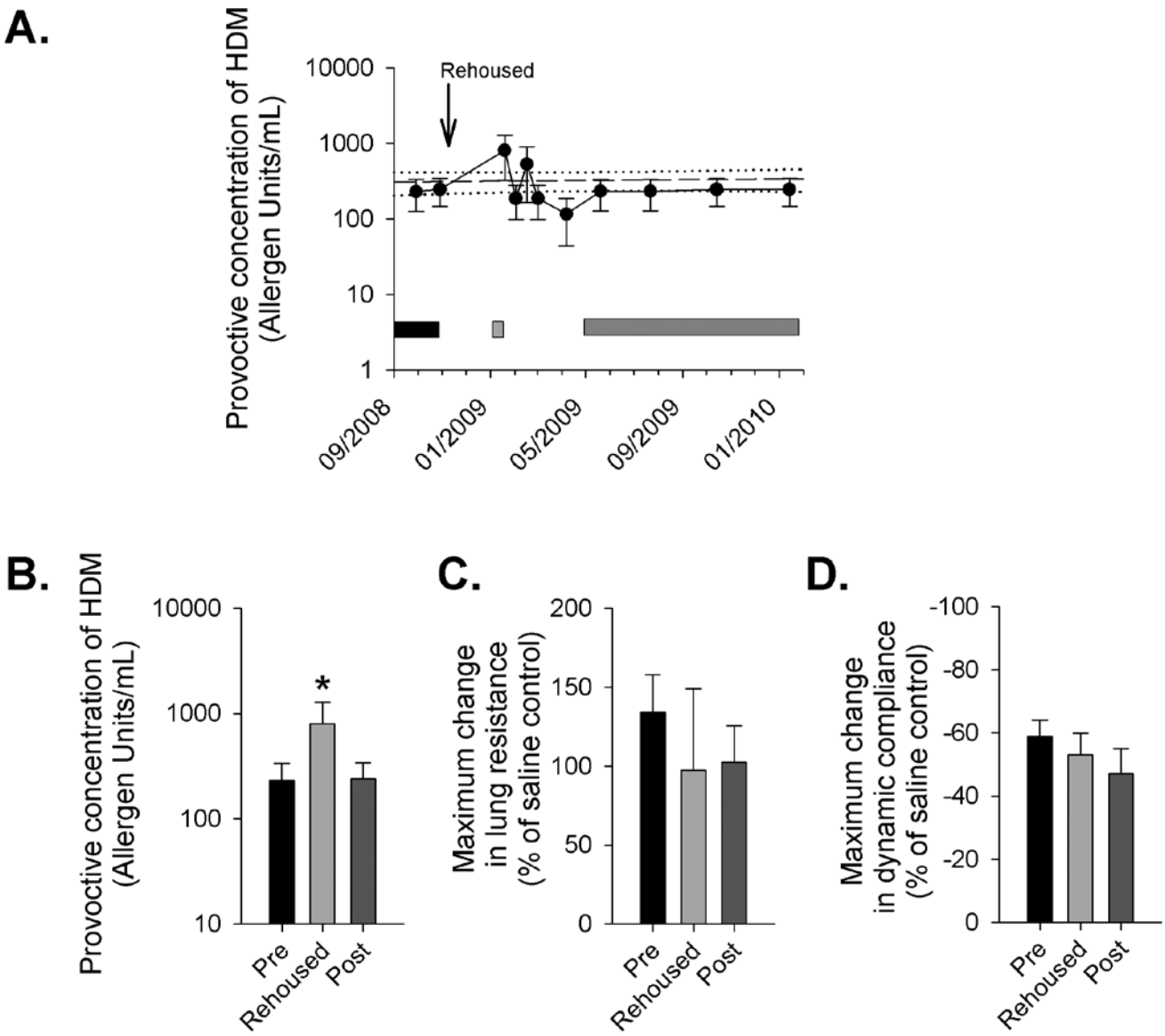

Figure 2. Effect of rehousing on HDM responses. Here 7 adult allergic macaques previously housed in the same room were moved into a new room in which 4 of the macaques were placed in a gang cage. No other macaques were involved in the room change. (A) Provocative concentrations of HDM required to induce target changes in lung resistance and dynamic compliance before and after the room change. The regression line (dashed line) and 95% confidence interval (dotted lines) based on data from the entire time period are shown. (B) The provocative concentration of HDM aerosol and maximal changes in (C) lung resistance and (D) dynamic compliance before (Pre), during the first challenge after (Rehoused), and 7 to 15 mo after the room change and caging reconfiguration (Post) are plotted. Values are presented as mean ± SE ($n = 7$). *, The provocative concentration of HDM before the housing reconfiguration is significantly ($P < 0.05$; repeated-measures ANOVA) lower than that at the first challenge thereafter.

Corticosteroids are potent inhibitors of pulmonary responses to allergen, and accordingly, mice, rats, and guinea pigs exhibit reduced allergic inflammation and airway hyperresponsiveness in response to acute stress.[22] Cortisol levels in rhesus macaques have been shown to remain elevated at 14 wk after their relocation to new housing.[11] This prolonged elevation of cortisol is consistent with the increase in PC_{HDM} associated with rehousing and changes in group structure in our macaques. Furthermore, changes in mitogen stimulation and lymphocyte proliferation after destabilization of social conditions is dependent on the degree of affiliation among members in the group.[9] Differences in the strength of affiliation could explain our observation that 2 macaques from the same group that normally exhibit a high degree of affiliation exhibited parallel changes in HDM responses when one of them was temporarily removed from the group (Figure 3 A). In contrast, a macaque with relatively low affiliation with group members was not affected by separation. Others have shown stress can be beneficial or harmful or enhancing or suppressive, depending on the type of immune response that is affected.[12]

Interestingly, the change in response to HDM was prolonged compared with the apparent duration of the stress. For example, the separation of a macaque from its group for a single evening during a telemetry protocol resulted in altered responses to HDM for more than 2 mo (Figure 3). Similar observations have been made regarding rhesus macaques in response to rehousing[14,15] The dominance hierarchy was reestablished without aggression in about 48 h, yet differences in circulating $CD4^+$ and $CD8^+$ T lymphocytes were present for as long as 9 wk. Therefore, in both cases, a relatively brief event precipitated a

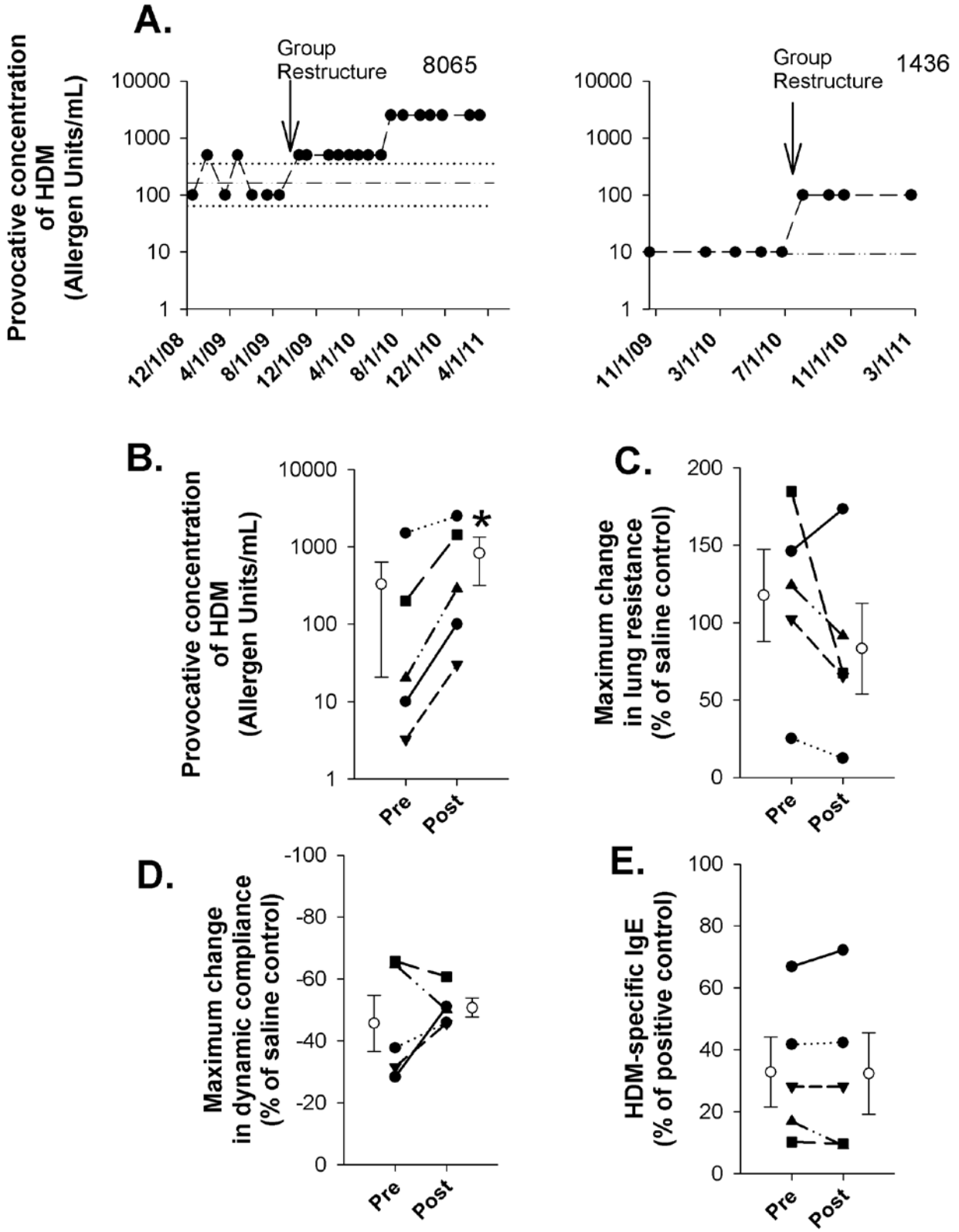

Figure 3. Effect of restructuring social groups on HDM sensitivity. (A) Representative tracings from 2 macaques (left, juvenile male; right, adult female) housed in different social groups that underwent restructuring. The regression line (dashed line) and 95% confidence interval (dotted lines) for the data collected before rehousing occurred are shown. (B through E) HDM responses for 5 macaques from 2 different groups that underwent restructuring. Data shown are those for individual macaques and the group means (± SE) immediately before and after restructuring (that is, during 8 wk of the event). (B) The provocative concentration of HDM is significantly (*, $P < 0.05$ by Student paired t tests) higher after restructuring of the groups. (C) Lung resistance, (D) dynamic compliance, and (E) plasma HDM-specific IgE levels before and after the restructuring did not differ.

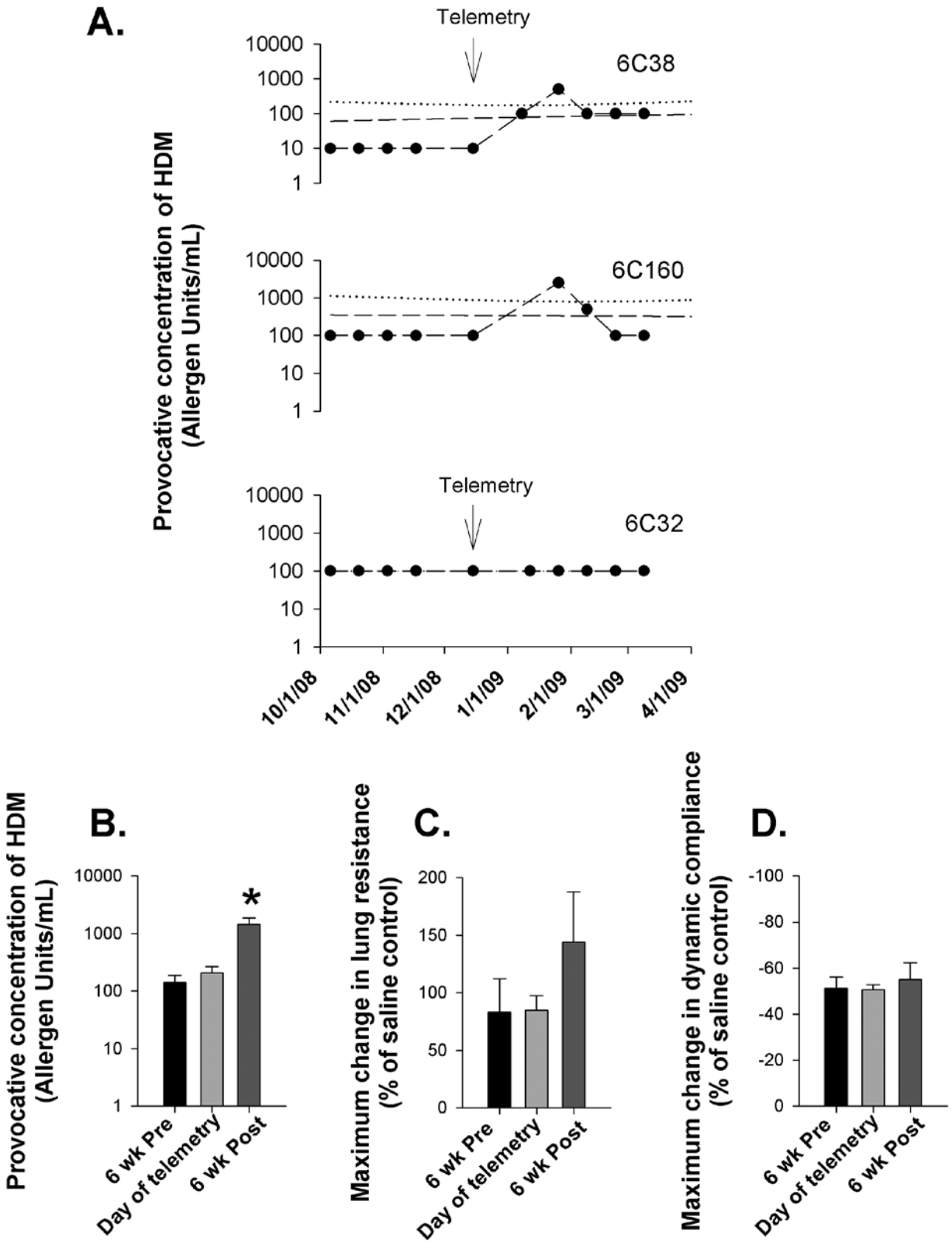

Figure 4. Effect of a telemetry protocol requiring overnight isolation of individual macaques. Here 13 allergic macaques from diverse social groups across the colony were enrolled in a study that required them to wear a telemetry jacket overnight, during which time they were separated from their social group by using tactile screens. (A) Representative tracings from 3 cagemates: 6C38, who wore a jacket and showed a decrease in allergic sensitivity; 6C32, who wore a jacket and did not exhibit a decrease in HDM responses; and 6C160, who neither wore a jacket nor was separated from the cohort but still exhibited a decrease in sensitivity. Regression lines (dashed lines) and the upper 95% confidence limits (dotted lines) for the data collected throughout the dates are shown. The (B) provocative concentration of aerosolized HDM and maximal changes in (C) lung resistance and (D) dynamic compliance for the last reading before the telemetry protocol (Pre), the day the protocol was implemented for each macaque, and the first HDM response after the protocol (Post) are plotted. *, The provocative concentration of HDM was significantly ($P < 0.05$, ANOVA) higher soon after the telemetry session, compared with those of the 2 recording periods before the session.

response lasting more than 2 mo. This finding is consistent with those regarding Old World monkeys, in which, in particular situations, adaptation to separation or relocation might be delayed until 1 to 5 mo after the change in environment.[5]

In contrast to acute stress, long-term stress in rodents and humans can accentuate airway inflammation and bronchoconstriction.[22] All events in the present study attenuated the allergic asthma phenotype, with no indication of augmentation. Two factors may contribute to the lack of augmented allergic responses in the current study. First, the social groups in this colony are relatively stable, and the effect of social stress in rhesus macaques is known to be attenuated when the stressed animals remain within an otherwise stable group, as compared with that in subjects that experience stress alone.[13] As stated previously, even in cases in which new groups are formed, a new dominance hierarchy can be established relatively quickly and without aggression. A second factor is that the macaques in the present study were only exposed to allergen at 6- to 8-wk intervals and the allergen challenges were not superimposed on the psychosocial stressor. In fact, standard operating procedure in the facility is that changes in housing, enrichment, and husbandry are implemented at times during which allergen challenges are not planned to occur. Superimposing exposure to asthma triggers on the stress response, as is common in humans, might result in a different outcome. Effects of social complexities and stress on experiments has been documented to occur in rodents as well.[18]

The current study was retrospective, thus limiting conclusions regarding the association between variables as compared with causation, but several observations led to the idea that changes in social environment induced stress, which then altered responses to HDM. First, in the absence of a change in the social environment, responses to allergen were quite consistent. This consistency was evident for the whole colony, as well as for individual macaques, as indicated by the stability in the data prior to an event. In contrast, an abrupt change in the response was observed during a subsequent allergen challenge and, in most cases, occurred during the challenge that immediately followed the change in social environment. Second, changes in the social environment resulted from a variety of circumstances, each of which was reproduced in different groups, at different times, and in different locations but with the same effect on responses to allergen. Furthermore, not all macaques in the various groups responded to the environmental changes, thereby reducing the possibility of systematic error. Third, an unbiased approach was used to identify events associated with changes in allergic responses. Deviation in a macaque's normal response to allergen was identified, records associated with clinical and experimental interventions were excluded, and then recorded events preceding the changes were identified. Thus, the precipitating events were identified in a blinded fashion, solely on the basis of changes in pulmonary function, yet the precipitating events were remarkably consistent in regard to their ability to induce psychosocial stress in this species. Although a specific mediator was not identified and remains to be determined, it is highly likely that the changes in social environment identified in the current study led to psychosocial stress that affected these macaques' responses to aerosolized allergen.

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