ORIGINAL ARTICLE

Hypercortisolism Associated With Social Subordinance or Social Isolation Among Wild Baboons

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Background: The phenomena of basal hypercortisolism and of dexamethasone resistance have long intrigued biological psychiatrists, and much is still unknown as to the causes and consequences of such adrenocortical hyperactivity in various neuropsychiatric disorders. We have analyzed basal cortisol concentrations and adrenocortical responsiveness to dexamethasone in a population of wild baboons living in a national park in Kenya. We tested whether social subordinance in a primate is associated with dexamethasone resistance. Furthermore, we examined whether individual differences in adrenocortical measurements were predicted by the extent of social affiliation in these animals.

Methods: Seventy yellow baboons (*Papio cynocephalus*) were anesthetized and injected with 5 mg of dexamethasone; the cortisol response was monitored for 6 hours. The animals were of both sexes in a range of ages and had known ranks in the dominance hierarchies within their troops. Extensive behavioral data were available for a subset of 12 adult males who were anesthetized under circumstances that also allowed for the determination of basal cortisol concentrations.

Results: The socially subordinate baboons were less responsive to dexamethasone than were the dominant ones; as one manifestation of this, postdexamethasone cortisol values were more than 3 times higher in the dozen lowest-ranking animals compared with the dozen highest. In addition, socially isolated males had elevated basal cortisol concentrations and showed a trend toward relative dexamethasone resistance.

Conclusions: Our findings indicate that social status and degree of social affilitation can influence adrenocortical profiles; specifically, social subordinance or social isolation were associated in our study with hypercortisolism or feedback resistance.

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GLUCOCORTICOIDS, the adrenal steroids secreted in response to stress, are critical for the successful adaptation to acute physical stressors. However, hypersecretion of glucocorticoids can have deleterious effects on immune defenses, metabolism, reproductive physiology, tissue repair, and neurologic status.[1] As such, it is not surprising that there exists a complex array of neuroendocrine regulatory mechanisms to maintain glucocorticoid concentrations within a desirable range,[2] and the failure of such regulation in some neuropsychiatric conditions is worth examining.

Hypercortisolism (taking the form of basal hypersecretion of cortisol and/or manifestations of glucocorticoid feedback resistance) occurs in approximately half of the individuals with primary affective disorders.[3] In addition, hypercortisolism occurs in individuals with anorexia nervosa[4] and Alzheimer disease,[5-7] aging humans in general and those aging "unsuccessfully" in particular,[8-10] individuals of varying maladaptive coping styles,[10-12] and chronically stressed individuals.[13-15] Despite this wealth of correlations, it remains unsettled precisely what psychological traits or disease subtypes are most likely to give rise to hypercortisolism, what pathophysiologic consequences it might have, and what prognostic value it might serve.

A cornerstone of much basic research in biological psychiatry is that there is considerable homology in the psychobiology of human and nonhuman primates, allowing more confident generalizations between them than between humans and other species. To that end, one of us (R.M.S.) has studied the psychoendocrinology of a population of

SUBJECTS AND METHODS

Background on baboon life histories and social organization research was conducted on yellow baboons (*Papio cynocephalus*) in Amboseli National Park, a semiarid savanna in southern Kenya, during 1989 and 1990. Baboons are among the largest, most sexually dimorphic, and most ground-dwelling monkeys. They live in semiclosed matrilocal social troops consisting of males and females of all ages. Baboons are omnivores that forage long distances daily. Detection of and protection from predators is such an important benefit of troop living for these animals that individual baboons make extreme efforts to remain with their troop, even shortly after parturition or when encumbered by illness or aging.

Like most anthropoid primates, female baboons stay in their troop of birth throughout their lives and, from about 6 years of age, produce a single infant per gestation at 1- to 2-year intervals. After a subadult period, from 6 to 8 years of age, most males leave their natal troop and, if successful, reproduce in 1 or a succession of other troops; immigration is mostly into nearby troops.[20] Under stable demographic conditions, animals older than 6 years usually constitute half of the 60 or so animals in a troop, and a few of each sex are usually older than 16 years.[21-23]

SUBJECTS

We studied adult and juvenile baboons in 3 social groups in and around Amboseli National Park.[24,25] This population has been under continuous, near daily, observation since 1971,[26-29] resulting in extensive information on demography, life history, reproductive behavior, and agonistic and affiliative interactions. The animals were individually recognized and habituated to observers. Two of the study groups (the Hook group and the Alto group) subsist entirely on wild foods; the third group (the Lodge group) partially forages at a garbage dump adjacent to a tourist lodge. The difference in food source affects time spent in various activities,[30,31] body size and composition,[32] and energy expenditure (but not intake) for adult females.[30,31]

For baboons born into the study groups, birth dates were known to within a few days.[33] For males who first appeared in the study groups as subadults or adults, birth-date estimates were made on the basis of patterns of physical growth, testicular enlargement, and on other physical characteristics, the scoring for which was developed by assessing known-age males and by observing aging patterns in long-term members of the population.[29]

METHODS

Determination of Dominance Rank

The baboons in the study groups were assigned dominance ranks within their age-sex classes. Agonistic behaviors were recorded ad libitum as part of routine monitoring and were defined according to Hausfater.[34] Based on these interactions, the animals were assigned rank numbers according to the number of animals within their age-sex class with whom they lost agonistic encounters. Thus, for example, an adult female of rank 4 consistently lost encounters with just 3 adult females and won encounters with all other adult females. Rank relationships were virtually always linear. Rank relationships among adult females are usually stable over many years[35]; those of adult males and juveniles are age-dependent and change more often.[29,36,37]

Determination of Social Connectedness and Social Isolation

In addition to routine data collection on life history, demography, reproductive behavior, and dominance rank, detailed data about adult male social behavior were collected by one of us (S.C.A.) during the 2 months prior to darting for anesthetization. These data were collected as part of a larger multiyear study about adult male baboon social behavior and presented an opportunity to examine detailed social correlates of hypercortisolism for the subset who were successfully darted (n=12). A total of 40 hours of observational data were collected about these animals during 40-minute focal animal samples[38] between 8 AM and 4 PM, excluding noon. All affiliative and agonistic interactions, as well as the identity of interactant, were recorded. Data about the number of "neighbors" (other baboons within 3 m) were collected as instantaneous scan samples[38] every 2 minutes during the focal sample. Data were also collected on sexual consortships obtained by each male. Consortships are periods of close, persistent following and guarding of an adult estrous female and are the typical mating pattern for this species.

A set of 8 social measurements deemed to be representative of the entire spectrum of male social interactions was extracted from these data. These measurements included rates of affiliative interactions per hour with adult females and adult males, rates of agonistic interactions per hour with adult males and adult females, proportion of time spent in social proximity (ie, other baboons within 3 m of the subject), average number of baboons within 3 m (neighbors) during periods when the subject was not alone, number of reciprocal grooming relationships (in which the subject was the groomer as often as was groomed), and the proportion of available sexual consortships with adult females obtained by the subject. This was calculated as that male's proportion of the total hours of consortships in the group during that 2-month period.

For each male, a cumulative measurement of "social connectedness" was calculated as the subject's deviation from the median for each of these 8 behaviors:

$$S = \frac{\sum_{i=1}^{8} \frac{x_i}{\text{Median}_i}}{8}.$$

wild olive baboons (*Papio anubis*) living freely in a national reserve in East Africa. These studies produced indirect evidence for dexamethasone resistance in socially subordinate baboons in that subordinance was associated with basal hypercortisolism,[16] which was, in turn, associated with dexamethasone resistance.[17] Moreover, an absence of social affiliation among dominant males was associated with basal hypercortisolism as well.[18,19] In this article, we expand on these findings in many ways. First, we examine these issues in a different species of baboon. Second, we test directly, for the first time, whether social subordinance in a primate is associated with dexamethasone resistance. Finally, we examine the relationship between adrenocortical end

The result was an index for each subject of whether male was on average above or below the median value for social connectedness. Scores above 1 indicated males with more social interactions and a richer social environment than average; scores below 1 indicated males with a relative lack of social interaction.

Acquisition of Blood Samples

Plasma was obtained by anesthetizing subjects with 75 mg of tiletamine hydrochloride and 75 mg of zolazepam hydrochloride (Telazol) per animal (male weight range, 16-38 kg; female weight range, 10-24 kg) injected from a propelled syringe fired from a blowgun at 10 m. No pregnant females beyond the first trimester were darted. Time constraints made it impossible to dart all of the baboons in the study groups. We attempted to maximize the representation of adults in the sample, but it was impossible to be selective while darting; instead, we darted opportunistically, anesthetizing the animals only when their backs were turned, to preclude anticipatory stress, and when the attention of other group members was elsewhere. Thus, the sample represents most of the adult males, many of the nonpregnant adult females, and a smaller representation of juveniles. The Lodge group is most heavily represented because they were the largest, most accessible group. All subjects were darted between 7:30 AM and 10:30 AM during the summers of 1989 and 1990 to control for seasonal and circadian hormone fluctuations. Blood samples were obtained at the earliest opportunity after the baboons became unconscious, which was within 12 minutes. The subjects were kept anesthetized throughout the procedure. Reanesthetization was carried out when movement and muscle tension precluded obtaining a blood sample or the animal resting safely. This typically resulted in redosing with 25 mg of tiletamine hydrochloride approximately every 2 hours until the completion of the experiment, at 7 hours. Subjects recovered in a cage near their group and were released when fully conscious the next morning. The animals did not lose habituation to observers or experience difficulty in rejoining the groups. There was no relationship between basal cortisol concentrations and the time of day of darting ($r=0.06$, $P=.75$), precluding the possibility of a circadian confound (eg, that less socially affiliated baboons were easier to dart and, thus, were sampled closer to the circadian peak).

Dexamethasone Suppression Test

A second blood sample was obtained 1 hour after the initial darting. Immediately following that, 5 mg of dexamethasone (Decadron phosphate) was administered to the animals intramusclarly and subsequent samples were obtained 3 and 6 hours later (4 and 7 hours postdarting). Thus, this protocol differs from the classic dexamethasone suppression test.[39] First, of necessity, the animals had to be anesthetized throughout. Second, the 7-hour postdarting sample represented the latest time point at which samples could be obtained for the animals to still safely recover by the next morning; thus, the lengthy postdexamethasone follow-up done in the typical dexamethasone suppression test could not be carried out. Finally, an extremely large concentration of dexamethasone was used (approximately 15-fold higher on a body weight basis than in the standard 1-mg human protocol); this was to induce feedback suppression of the adrenocortical axis within the limited time available for monitoring the animals. This protocol was suppressive within this period in a previous study with wild baboons.[17] This modified dexamethasone suppression test was carried out on 70 animals.

Assay of Cortisol Concentrations

Samples were centrifuged on site and plasma was frozen in dry ice until they were returned to the United States. Cortisol concentrations were determined by radioimmunoassay[28] with an antibody with less than 0.1% cross-reactivity with dexamethasone (antibody F21-53, Endocrine Sciences, Tarzana, Calif). Intra-assay and interassay coefficients of variation were 0.07 and 0.11, respectively.

STATISTICAL ANALYSIS

In our studies correlating basal cortisol concentrations with a number of behavioral measurements, baboons were excluded from analysis if the initial "basal" sample was collected more than 15 minutes after darting. This was because our prior studies with chair-restrained, catheterized baboons[16] indicated that cortisol concentrations had probably elevated markedly in those samples from true basal values.

Statistical procedures were performed using a statistical software package (JMP 3.0, SAS, Cary, NC).[40] For initial analyses, data were pooled across social groups. Among these baboons, garbage feeding was associated with markedly higher rates of aggression,[41] probably associated with intense competition for a highly localized food resource. Thus, we also analyzed data as a function of membership in the wild-feeding group vs the higher aggression, garbage-feeding group. Descriptive statistics were obtained for cortisol concentrations at darting and at 1, 4, and 7 hours after darting. A single classification analysis of variance was used to determine whether cortisol concentrations changed significantly over time. Simple linear regressions were employed to examine the effects of social connectedness on basal cortisol concentrations and on dexamethasone responsiveness, which is defined as the circulating cortisol concentrations 6 hours after dexamethasone administration. Previous work on this population has shown that the incidence of hypercortisolism increases with age.[28] Therefore, multiple regressions were employed to examine the effects of social rank and age on basal cortisol concentrations and on dexamethasone responsiveness.

points and social affiliation in more behavioral detail and over the entire rank range.

RESULTS

Six hours of dexamethasone exposure caused a significant decline in cortisol concentrations ($F[3, 235]=4.8$, $P<.01$) (**Table 1**). Such dexamethasone responsiveness occurred in both sexes and both feeding conditions (Table 1). This seemed to represent a true suppression by dexamethasone, rather than the normal circadian decline in concentrations that occurs at that time of day or the inhibitory effects of the benzodiazepine zolazepam contained in the anesthetic. As evidence, under iden-

Table 1. Cortisol Concentrations After Darting With Anesthesia and After Administration of Dexamethasone*

Time, h†	All Subjects (N=33-70)	Wild Diet		High Aggression‡	
		Female (n=24-28)	Male (n=9-14)	Female (n=8)	Male (n=9-10)
1	500±40	440±80	80±110	470±80	410±110
4	360±30	360±60	390±80	330±60	410±60
7	300±30	300±80	330±110	330±60	250±80

*Data are expressed as nanomoles per liter (±SEM). Sample size varied because of the exigencies of field conditions (ie, it might be impossible to obtain a correctly timed sample on an animal if a second animal had been darted and was being tracked in the bush).

†Time indicates hours after darting and anesthesia. Dexamethasone was administered immediately after the 1-hour sample.

‡High agression indicates the garbage-feeding group.

tical darting and anesthetization conditions without dexamethasone, cortisol concentrations increased to 860±60 nmol/L (mean±SEM) in wild baboons by the 6-hour mark.[42]

Basal cortisol concentrations were not predicted by dominance rank; however, social connectedness was a strong predictor of such concentrations. Specifically, for the 12 males from whom we had data on social connectedness as well as basal cortisol concentrations, socially isolated males had significantly higher basal concentrations than males that were well-connected socially (R^2=0.50, P=.01, n=12) (**Figure 1**). Age did not contribute to the variance in basal cortisol concentrations when it was included in a multiple regression with social connectedness (R^2 [adjusted]=0.39, P=.04, n=12). This is a somewhat weaker regression than the linear regression of basal cortisol concentrations on social connectedness alone.

Dexamethasone responsiveness declines with age in this population of baboons.[28] A multiple regression revealed that social rank as well as age predicted dexamethasone responsiveness (R^2 [adjusted]=0.15, P=.002; partial F for social rank=6.00, P=.017; partial F for age=7.01, P=.01) (**Figure 2**). Specifically, the more socially subordinate an individual baboon, the higher its cortisol concentrations 6 hours after dexamethasone administration. As one manifestation of this, cortisol concentrations were more than 3 times higher in the dozen lowest-ranking animals compared with the dozen highest. This relative dexamethasone resistance occurred in subordinate animals in both feeding conditions, with the effect being stronger for animals from the high-aggression, garbage-feeding group and for those animals when divided by sex (**Table 2**). The relative dexamethasone resistance among subordinate animals probably does not reflect the stress of nutritional deprivation; as evidence, socially subordinate adult females do not weigh less than their high-ranking counterparts (r=−0.12, P=.68).

For the 12 males for whom we had data about social connectedness, dexamethasone responsiveness showed a nonsignificant tendency to decline with increasing social isolation. Males below the median for social connectedness had postdexamethasone cortisol concentrations 2-fold higher than males above the median for social connectedness (650±210 nmol/L vs 300±210 nmol/L; P<.20, unpaired t test). There was no correlation between rank and social connectedness (r=−0.24, P=.44).

COMMENT

In our study, we observed that social subordinance and social isolation are associated with manifestations of hypercortisolism in wild baboons. Specifically, socially subordinate animals were less responsive to dexamethasone than were dominant animals; to our knowledge, this is the first explicit demonstration of this with a social primate. Moreover, socially isolated males had elevated basal cortisol concentrations and a trend toward relative dexamethasone resistance.

The linking of dexamethasone resistance with social subordinance coincides with knowledge about the effects of chronic stress on glucocorticoid secretion. In the adrenocortical axis, elevated circulating glucocorticoid concentrations exert a negative feedback effect, inhibiting subsequent secretion.[2] Repeated stressors can cause glucocorticoid feedback resistance in rodents,[43-45] primates,[46,47] and humans.[13-15] Moreover, the onset of affective disorders involving dexamethasone resistance is often preceded by major stressors.[48] In stable dominance hierarchies among baboons (as were the ones studied), subordinance is associated with far more stressors than is dominance (a situation that is quite different in unstable, shifting hierarchies). Dominant animals have the lowest rates of aggression, are rarely challenged by subordinates, and have highly predictable control over resources and sources of social support. In contrast, subordinate animals have the highest rate of losses in agonistic interactions, have reduced feeding efficiency (at least partly because of interference by high-ranking males[49,50]), and reduced access to favored resources.[49,51-53] They are also subject to the highest rates of displaced aggression and disruption of social grooming; the stressfulness of such unpredictable events is well documented.[54] The social rank–dexamethasone responsiveness link was particularly strong in the group that had higher rates of aggression than in the other 2 groups.[33] This aggressiveness is most likely owing to that group's subsisting on garbage, which entails intense competition for localized food resources, an association long recognized in troop-living primates.[55,56]

Dominance systems among yellow baboons differ by sex. Male social rank changes frequently as males age and migrate between groups, which they do periodically.[29,37] In contrast, females remain in their natal group throughout their lifetime and inherit dominance rank from their mothers.[36] The linking of dexamethasone resistance to social subordinance in these 2 different dominance systems as well as to 2 distinct feeding conditions suggests it is a rather robust association.

Our study offers no data regarding the neuroendocrine mechanisms of hypercortisolism or dexametha-

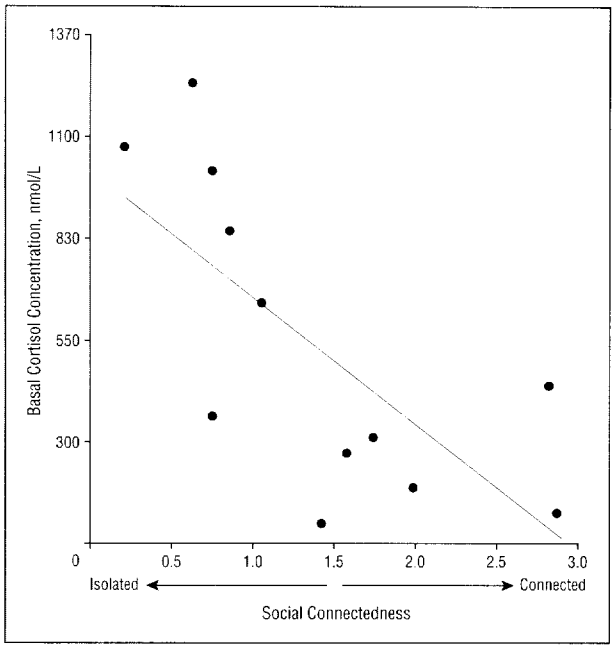

Figure 1. *Basal cortisol concentrations were predicted by social connectedness for adult males (R^2=0.50, P=.01, n=12). Each dot represents the value for 1 baboon. Social connectedness is an index of the extent to which males score high (connected) or low (isolated) on 8 social measurements; measurements of social connectedness were available for 12 males.*

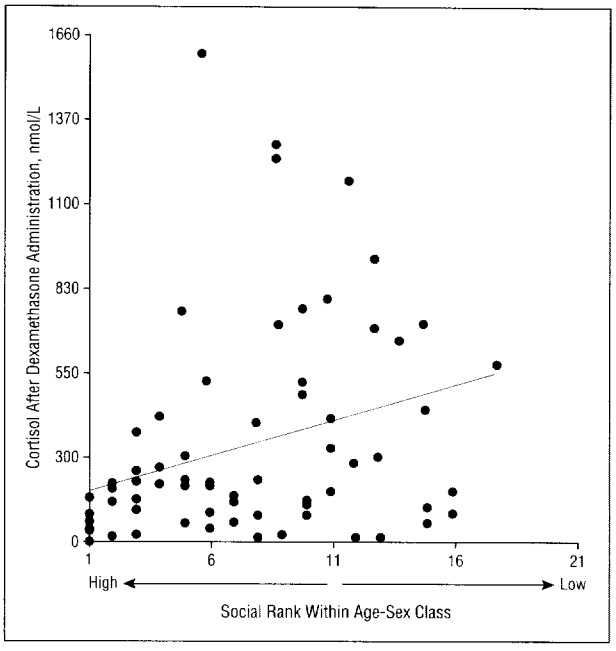

Figure 2. *Dexamethasone resistance (circulating cortisol 6 hours after dexamethasone administration) was predicted by social rank. Each dot represents the value for 1 baboon. Because previous work on this population had shown that the incidence of dexamethasone resistance increases with age, we included age and social rank in a multiple regression analysis of dexamethasone resistance (R^2 [adjusted]=0.15, P=.002, n=70)(Table 2). The fitted line in the Figure corresponds to a simple linear regression of dexamethasone resistance on social rank (R^2=0.09, P=.011, n=70).*

sone resistance; however, some laboratory data are relevant. Sustained or repeated stress can down-regulate (decrease) glucocorticoid receptor numbers and levels of receptor messenger RNA in rodents[57-59] and primates.[60] This is particularly pronounced in the hippocampus. This structure, in turn, helps mediate glucocorticoid feedback regulation, inhibiting subsequent glucocorticoid secretion.[61] Down-regulatory loss of hippocampal glucocorticoid receptors weakens such feedback regulation, producing feedback resistance.[62] These data, derived primarily from rodents, may apply to primates in that dexamethasone resistance, depletion of glucocorticoid receptors in the hippocampus, and a history of social instability have been linked in macaque monkeys.[47] In that context, it was surprising that the feedback resistance of the subordinate animals did not also involve basal hypercortisolism, a feature seen among subordinate animals in many, but not all, social species and populations (including the closely related olive baboon[63]). However, basal hypercortisolism and dexamethasone resistance can dissociate in human depressives.[3]

We observed that social isolation was also associated with hypercortisolism, manifesting itself as elevated basal cortisol secretion and a trend toward dexamethasone resistance. In a previous study with a wild population of closely related olive baboons (*P anubis*), we observed that among dominant males, those with the lowest rates of grooming with females and social interactions with infants had markedly elevated basal cortisol concentrations[18,19]; the present data show the link between social isolation and hypercortisolism in greater behavioral detail. These studies cannot reveal whether there is any causality in this link (ie, if hypercortisolemia makes animals less socially affiliated or if social isolation stimulates adrenocortical secretion). However, studies with rodents and captive primates demonstrate the power of social proximity or affiliation to blunt the adrenocortical response to various stressors,[54] suggesting that these baboons are hypercortisolemic because they lack the stress-reducing advantages of social affiliation. This notion is supported by studies on the role played by dominance interactions and social affiliation in reducing social tension and maintaining cohesion in the social group.[64]

This association echoes the classic finding in behavioral medicine that social isolation represents a highly notable mortality risk factor across a wide range of maladies in humans[65] (although the effects of social isolation

Table 2. Results of Multiple Regressions of Dexamethasone Responsiveness on Age and on Social Rank Within Age-Sex Class

Conditions	No. of Subjects	R^2 (Adjusted)	P
All conditions pooled	70	0.15	.002
High-aggression garbage feeders			
Sexes pooled	28	0.34	.002
Females only	10	0.72	.005
Males only	18	0.29	.03
Wild feeders			
Sexes pooled	42	0.11	.04
Females only	14	0.01	.38
Males only	28	0.11	.09

on adrenocortical profiles have not, to our knowledge, been studied systematically in humans). A key finding in those studies was that no particular form of social affiliation (a spouse, a close friend, or strong involvement in a community group) was more protective than the others, but that the association instead emerged from the aggregate of social connections of an individual baboon. Similarly, we did not observe any single 1 of the 8 measurements of social connectedness to predict adrenocortical status; instead, it was their aggregate that was highly predictive.

CONCLUSIONS

The challenge remains in biological psychiatry to understand the causes and consequences of hypercortisolism. Classic studies of the parents of children with cancer demonstrated that the adrenocortical axis responds to external stressors (such as the illness) and internal coping styles.[11] Our study repeats this theme in showing the relevance of the external factor of rank and an individual's affiliative style. When coupled with other studies showing adrenocortical correlates of personality styles in nonhuman primates,[18,19,66] our findings emphasize the relevance of such studies to understanding the behavioral biology of humans as well as the subtle complexity of these animals in their own right.

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