

Cerebrospinal Fluid Monoaminergic Metabolites Differ in Wild Anubis and Hybrid (*Anubis hamadryas*) Baboons: Possible Relationships to Life History and Behavior

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This article reports monoaminergic metabolite [homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylglycol (MHPG)], values from the cerebrospinal fluid (CSF) of 27 wild baboons (Papio hamadryas) aged 40 to 140 months. Animals were either anubis, or anubis with hamadryas admixture; males of the latter subspecies generally have a reduced tendency to disperse from their natal groups. Overall, the values and interrelationships among the CSF monoamine metabolites resembled data reported from closely related, captive-housed animals. For example, age was significantly correlated with HVA concentrations ($r = -60, p < .05$), but not with the other metabolites. Notably,

males characterized by hamadryas admixture had significantly higher concentrations of HVA, 5-HIAA, and MHPG ($p < .05$, respectively), a result possibly driven by differences in serotonergic activity. These data provide initial evidence that variation in central monoaminergic activity, as indicated by CSF monoamine metabolite concentrations, may reflect differences in behavior and life history that have taxonomic and, perhaps, evolutionary significance. [Neuropsychopharmacology 20: 517–524, 1999] © 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.

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There is increasing interest in the neurobiologic factors underlying variation in social behavior, both among individuals and between species (Clarke and Boinski 1995; Young et al. 1997). Among such factors, considerable attention has focused on the relationship between behavioral characteristics and the monoaminergic neurotransmitters (serotonin, dopamine, and norepinephrine) (Kraemer and Clarke 1996). Interest in these neurotransmitters stems, in part, from the suggestion that interindividual variation in their release or uptake might be under partial genetic regulation and thereby contribute to the enduring, trait-like behavioral differences often observed among individuals within groups of primates, both human and nonhuman (Zuckerman 1991; Mulder 1992; Cloninger 1994). An extensive literature documents the inverse association between indices

of serotonergic activity and aggressiveness in monkeys (Raleigh et al. 1986; Higley et al. 1992; Botchin et al. 1993), or violence and impulsiveness in human beings (Brown et al. 1982; Asberg et al. 1986; Linnoila et al. 1986; Berman et al. 1997; Manuck et al., 1998). Conversely, there are reports linking indices of elevated or high central serotonergic activity to positive social interaction in human subjects (Knutson et al., 1998) and monkeys (Raleigh et al., 1983; Botchin et al. 1993). Such behavioral relationships are of interest not only because of their impact on intragroup relationships but also because they might represent strategies having life history consequences. Supporting the latter suggestion are two reports linking high serotonergic activity to delayed dispersal of free-ranging male rhesus macaques (*Macaca mulatta*) from their natal groups (Kaplan et al. 1995; Mehlman et al. 1995).

The evaluation of neurotransmitter profiles seems especially useful in wild populations, where natural selective agents can unmask the fitness outcomes associated with behavioral variation and its neurochemical correlates or determinants. That such studies have not been done relates in part to the relatively invasive and demanding nature of the data collection. Monoaminergic activity in the central nervous system, for example, is often assessed in monkeys by measuring serotonergic, dopaminergic, and noradrenergic metabolite concentrations in cerebrospinal fluid (CSF). The CSF, in turn, is sampled from the cisterna magna, which requires placement of a needle through the dura into the subarachnoid space surrounding the brainstem. [The existence of a rostral-caudal gradient in the monoaminergic metabolites of serotonin and dopamine suggests that cisternal sampling provides a more accurate representation of brain monoaminergic turnover than can be obtained less invasively through a more caudal (e.g., lumbar) site (Gordon et al. 1975; Shelton et al. 1988)]. Finally, once collected, the CSF must be adequately preserved. The application of these procedures under field conditions is not trivial. As a result, virtually all knowledge concerning monoamine metabolites in nonhuman primates is currently derived from laboratory and captive colony settings (Shelton et al. 1988; Higley et al. 1992; Raleigh et al. 1992; Clarke et al. 1995; Kaplan et al. 1995). In addition to the above-referenced association between low serotonergic activity (as indicated by CSF metabolite concentrations) and early dispersal, these studies often report high correlations among the monoamine metabolites and a significant age-related decline in dopaminergic, and perhaps serotonergic, activity. It would be useful to determine whether such relationships extend to populations in their native habitat.

The foregoing considerations led us to undertake a pilot investigation evaluating the neurochemical profiles of anubis (*Papio hamadryas anubis*) and hamadryas (*P. h. hamadryas*) baboons. [The grivet monkeys (*Cerco-*

pithecus aethiops aethiops) that also live in the Awash Valley were subjected to a similar investigation; the results of this latter study are reported elsewhere (Fairbanks et al., unpublished results).] The two baboon forms differ significantly in social behavior as well as appearance. One distinction of potential interest with respect to central monoaminergic activity involves male dispersal. Like most macaques, anubis baboons live in multimale-multifemale troops characterized by almost universal male dispersal and strong female philopatry (Pusey and Packer 1987). In contrast, hamadryas males rarely move permanently from their natal group, or band, where they normally remain in close contact with male kin (their "clan") throughout their lives (Kummer 1968; Abegglen 1984; but see also Phillips-Conroy et al. 1992). Perhaps as a correlate of their philopatry, hamadryas males exhibit affiliative and mutually supportive behavior in a variety of social contexts in which anubis males tend to be indifferent or hostile to each other (Nystrom 1992).

These behavioral contrasts, and the existence of hybrids formed by interbreeding between the two baboon forms (Nagel 1973; Phillips-Conroy and Jolly 1986), suggested three objectives for a pilot study: (1) to establish the feasibility of collecting neurochemical data under field conditions; (2) to compare the monoamine metabolite values obtained from animals captured in their native habitat and natural social context with those reported from laboratory and colony populations; and (3) to conduct an initial test of the hypothesis that serotonergic metabolite concentrations would differ in the two parental baboon forms, and their hybrids, in ways consistent with the distinct behavioral characteristics of the parental populations. In this pilot study, sampling was limited to one anubis and one hybrid group. From the previously established relationship between dispersal and serotonergic activity in male rhesus, and the observation that the tendency to disperse in early adulthood is much less pronounced among hamadryas than among anubis males, we predicted that the level of serotonin metabolites in males with hamadryas admixture would be higher than in their "pure" anubis counterparts.

METHODS

Study Site and Animals

The study site was in the Awash National Park (ANP), approximately 200 km east of Addis Ababa, Ethiopia, within the East African Rift Valley. The altitude (about 1000 m above sea level) and natural vegetation of the park are intermediate between those of the Ethiopian high plateau and the semi-desert foothills and lowlands of the Danakil region (Jacobs and Schloeder 1993),

which are, respectively, typical anubis and hamadryas habitats. In the ANP, hamadryas baboon groups (about 100–150 animals) forage in palm groves and dry thornbush. The ranges of seven anubis baboon troops (15–120 animals each) are centered upon the narrow evergreen forest strip along the perennial Awash river (Nagel 1973; Phillips-Conroy and Jolly (1986; Jacobs and Schloeder 1993). A zone about 30 km wide between them is occupied by groups of baboons of intermediate appearance, evidently the product of hybridization. The Awash baboon populations have been sampled repeatedly by capture/release, as part of a long-term study designed to investigate morphologic, physiologic, and genetic variation. The 27 animals (22 males, 5 females) reported here are derived from an anubis group of about 60 animals, showing minimal hamadryas admixture (Group F) and a similarly-sized group consisting almost entirely of phenotypic hybrids (Group H) (Phillips-Conroy et al. 1992).

Trapping and Field Evaluation

All captures were made in the morning (between 6:00 and 11:00 A.M.), after several days of prebaiting (Brett et al. 1982). Animals were lured with corn into individual cage-traps that were closed manually by an observer. All of the adult male anubis were caught singly; a few adult male hybrids, however, were accompanied by one or even two other animals. Captives remained in the trap, untranquilized, for 10 to 120 min. They were then tranquilized, serially, with intramuscular ketamine administered via a pole syringe (10 mg/kg, weight judged by eye), and carried to a work site about 50 m away, where a variety of data and samples, including body weights and casts of the upper left dental quadrant, were collected according to an established protocol (Brett et al. 1982; Phillips-Conroy et al. 1992; Nystrom 1992). The age of each animal (in months) was estimated from its dental complement and from the degree of molar attrition visible in its dental cast, when compared with casts from a series from animals of known age (Phillips-Conroy and Jolly 1988; Phillips-Conroy and Bergman, in press). After sampling and examination, the animals were allowed to recover spontaneously, generally with 90 min of initial tranquilization. All recoveries were medically uneventful. Sampled animals (readily identifiable by their shaved napes) were seen to rejoin their social groups and were observed interacting normally on subsequent occasions.

Collection and Preservation of CSF

The animal to be sampled was placed on its right side, with the head flexed. The hair on the occiput was clipped, and the skin cleaned with alcohol followed by a betadine solution. A sterile 3-cc syringe was fitted

with a 25-gauge \times 2.5-inch needle. The needle was inserted at the point where the midline intersected a transverse line joining the cranial edges of the wings of the atlas. Slight suction was applied as the tip of the needle passed through skin, muscle, and fascia into the cisterna magna, and penetration of the subarachnoid space was detected by flow of CSF into the syringe. When approximately 1.5–3.0 ml of CSF had been obtained, suction was released, the needle carefully withdrawn, and the sample injected into a polypropylene vial containing 100 ng glutathione. The vials were placed in a wet cloth bag and allowed to cool by evaporation. Eight to 13 h later they were placed in liquid nitrogen and remained frozen until assay.

To determine the effect of short-term storage at ambient temperature, CSF samples were obtained from four adult male cynomolgus macaques at the laboratory of JRK. The samples from each animal were equally divided into four, 2.0-ml polypropylene vials. Following collection, one vial was immediately placed on dry ice, then frozen at -70°C . The remaining three vials, each containing 100 ng glutathione, were exposed to ambient summer temperatures ($23\text{--}29.6^{\circ}\text{C}$) for 8 h, then frozen at -70° . All of the samples were then analyzed by the techniques described in the Methods. The results indicated that there were no significant difference in monoamine metabolite concentrations (Frozen: 5-HIAA, 362 ± 51 [SEM] pmol/ml; HVA, 1324 ± 98 pmol/ml; MHPG, 50 ± 4 pmol/ml; Ambient: 5-HIAA, 343 ± 43 pmol/ml; HVA, 1370 ± 90 pmol/ml; MHPG, 57 ± 4 pmol/ml). Furthermore, the monoaminergic metabolite concentrations in the frozen samples were significantly correlated with those assayed in the samples that had remained at ambient temperature for eight h (5-HIAA: $r = 1.0$; HVA: $r = 1.0$; MHPG: $r = 0.95$).

Assessment of Monoamine Metabolites in CSF

All monoaminergic values reported and discussed here [collected from cynomolgus macaques (*Macaca fascicularis*) at Wake Forest University School of Medicine, Winston-Salem, North Carolina; rhesus macaques at Cayo Santiago, Puerto Rico; baboons at Southwest Foundation for Biomedical Research, San Antonio, Texas; as well as baboons at ANP] were assayed in the same laboratory by identical methods. As part of this method, a precisely measured aliquot of each sample was mixed with an equal volume of cold mobile phase. The mixture was then filtered by centrifugation (6000 g for 40 min at 4°C), and part of the filtrate transferred to a 300-FL microinjection insert. This material was then analyzed by high-performance liquid chromatography with electrochemical detection, according to the method of Scheinin et al. (1983). This allows simultaneous evaluation of the three major monoaminergic metabolites in CSF: (1) 3-methoxy-4-hydroxyphenylgly-

col (MHPG), the noradrenergic metabolite; (2) 5-hydroxyindoleacetic acid (5-HIAA), the serotonergic metabolite; and (3) homovanillic acid (HVA), the dopaminergic metabolite. The main source of 5-HIAA and HVA is the brain, as evidenced by the concentration gradient in CSF, and correlations between brain and CSF levels of 5-HIAA. MHPG does not have a concentration gradient and probably reflects contributions from blood and spinal cord. Although they generally reflect neuronal activity because a small proportion of released neurotransmitter is metabolized by monoamine oxidase after release and reuptake at the nerve terminal and before vesicular uptake, these metabolites are only indirect indices of neuronal activity because they are also affected by factors that alter catabolic rates independent of neuronal firing (Commissiong 1985).

Data Analysis

Before analysis, all metabolite values were subjected to a square-root transformation to normalize their distributions and reduce variance; however, only untransformed values are reported. In a further data transformation, we regressed the 5-HIAA values onto the HVA data and used the residuals so obtained as an "HVA-free" index of serotonergic activity. This was done because of the typically high correlation between CSF 5-HIAA and HVA and because of our hypothesis that serotonergic activity, in particular, would differ between the anubis baboons and those with hamadryas admixture. Preliminary analysis showed that the residuals were not significantly correlated with either HVA (by definition, $r_{27} = 0$) or MHPG ($r_{27} = 0.19$, NS).

Table 1. Central Monoaminergic Metabolites in Baboons Living in the Awash National Park^{a,b}

Monkey	Group	HVA	HIAA	MHPG	SEX	Age (months)
95002	F	411	76	50	M	100
95003	F	665	156	126	M	143
95004	F	1332	259	170	F	55
95005	F	819	183	102	M	170
95006	F	1259	245	164	M	52
95007	F	1100	214	188	M	66
95008	F	1321	231	234	M	76
95011	F	1162	213	185	M	68
95015	F	691	194	114	F	100
95016	F	1735	395	215	M	33
95020	F	1938	302	217	M	12
95021	F	1444	188	130	M	33
95023	H	904	196	172	M	98
95024	H	688	350	173	M	160
95027	H	1447	190	250	M	98
95028	H	1388	637	219	M	100
95029	H	2611	511	344	M	68
95033	H	2504	511	327	M	52
95034	H	1596	344	188	M	52
95035	H	911	266	168	M	180
95038	H	1184	292	168	M	68
95039	H	1233	294	170	M	57
95041	H	1492	297	255	F	180
95043	H	773	195	127	F	150
95044	H	1570	273	227	F	45
95045	H	1325	308	249	M	76
95046	H	1822	336	256	M	25
Mean values (\pm SEM)						
Awash baboons (27 baboons and females)		1308 (100)	283 (23)	192 (13)		
Cayo Santiago rhesus (60 adult males) ^c		1456 (55)	232 (9)	127 (4)		
Wake Forest Cynomolgus (4 adult males) ^d		1370 (90)	343 (43)	57 (4)		

^aTwo sets of male macaques included for comparison purposes.

^bMonoamine values in pmol/ml.

^cKaplan et al. 1995.

^dSee text for more detail.

The analytic strategy was as follows. Monoaminergic metabolites and age were first subjected to a correlation analysis. Values for adults were then compared by sex, without regard to group of origin (anubis or hybrid). Finally, hybrid and anubis males were compared by analysis of covariance (ANCOVA), using age as the covariate. All tests of significance were two-tailed.

RESULTS

Table 1 contains individual monoaminergic metabolite values and ancillary data from individual ANP animals together with the means (\pm SD) for the entire sample, by variable. For comparison purposes, this table also contains mean monoamine metabolite data collected from cynomolgus monkeys (*M. fascicularis*) in North Carolina under similar temperature conditions and from rhesus monkeys at Cayo Santiago (Kaplan et al. 1995). The 5-HIAA residuals are not included in Table 1, as they were calculated separately, depending upon which animals were involved in any particular analysis (e.g., all animals, all males). Table 1 indicates that monoamine metabolite values from the ANP baboons fell within the range observed in macaques, except for MHPG.

Table 2 shows the correlations among monoamine values and age for all animals ($n = 27$). The correlations among all of the metabolites are significant and high, as is the inverse correlation between HVA and age. Limiting the analysis to males did not alter the direction or strength of any correlation. Finally, a comparison (by ANCOVA with age as the covariate) between all males ($n = 22$) and all females ($n = 5$) revealed no significant differences for any metabolite, or for the 5-HIAA residual index ($F < 0.50$, NS). Nor were there any significant monoaminergic differences between the sexes when the analysis was limited to the eight males and three females that were all fully adult (> 96 months) ($F < 0.05$, NS).

We next compared monoamine metabolite values in males of all ages by group membership (anubis troop "F", $n = 10$; hybrid troop "H", $n = 12$) to test the prediction that hamadryas admixture in the hybrids would be

associated with altered central monoaminergic activity. There was no significant difference in mean age between males from F and H (Mean \pm SD = 75.3 ± 49.9 and 86.2 ± 45.1 months, respectively ($F < 0.5$, NS)). However, as indicated in Table 2, age showed a significant, inverse correlation with HVA and directionally similar correlations with the other metabolites. Furthermore, all of the monoamines were highly intercorrelated. Accordingly, an ANCOVA with age as the covariate was used for all comparisons between group F and H males. The results of these comparisons are depicted in Figure 1. Hybrid males exhibited significantly higher concentrations of each of the metabolites. The 5-HIAA residuals also differentiated the groups, and, since the residuals are uncorrelated with either HVA or MHPG, this effect is probably not driven by covariation with either of these metabolites.

DISCUSSION

The current investigation produced four major results. First is the practical demonstration that it is feasible to obtain CSF by cisternal puncture from fully wild animals at a remote field site, with no discernible adverse medical or behavioral effects upon the subjects, and that metabolite preservation comparable to that obtained under laboratory conditions can be achieved. Although cisternal CSF samples have previously been obtained outside of the laboratory (Higley et al. 1991; Kaplan et al. 1995), to our knowledge, this is the first time that they have been collected from wild animals. Preliminary experiments with CSF from macaques showed that the addition of glutathione to the sample tubes could prevent significant degradation of the monoamine metabolites, even at ambient temperatures comparable to those experienced at the field site. Though kept at ambient temperature for several hours before freezing, the ANP samples yielded metabolite concentrations within, or even slightly above, the range found in previous studies of nonhuman primates (Kaplan et al. 1994; Kaplan et al. 1995).

Second, our results, when compared with those of previous studies (Table 1), suggest an environmental effect on the CSF concentration of MHPG but not the other two metabolites. Specifically, MHPG was present in significantly higher concentrations among the ANP baboons than in indoor-housed *M. fascicularis* or free-ranging rhesus monkeys. In contrast, the other two metabolites fell within the range reported by us and others for macaques and vervets (Mehlman et al. 1995; Raleigh et al. 1992; Kaplan et al. 1995). It is tempting to dismiss the variation in MHPG concentration as due to differences among species or as artifacts of differential preservation. However, unpublished data from 91 adult male and female baboons housed in small groups at the

Table 2. Correlations Among All Animals ($n = 27$)

	HVA	HIAA	Residualized HIAA	MHPG	Age
HVA	—	0.71*	0.00	0.86*	-0.60*
5-HIAA		—	0.70*	0.75*	-0.23
Residualized HIAA			—	0.19	-0.27
MHPG				—	-0.32
Age					—

* $p < .001$

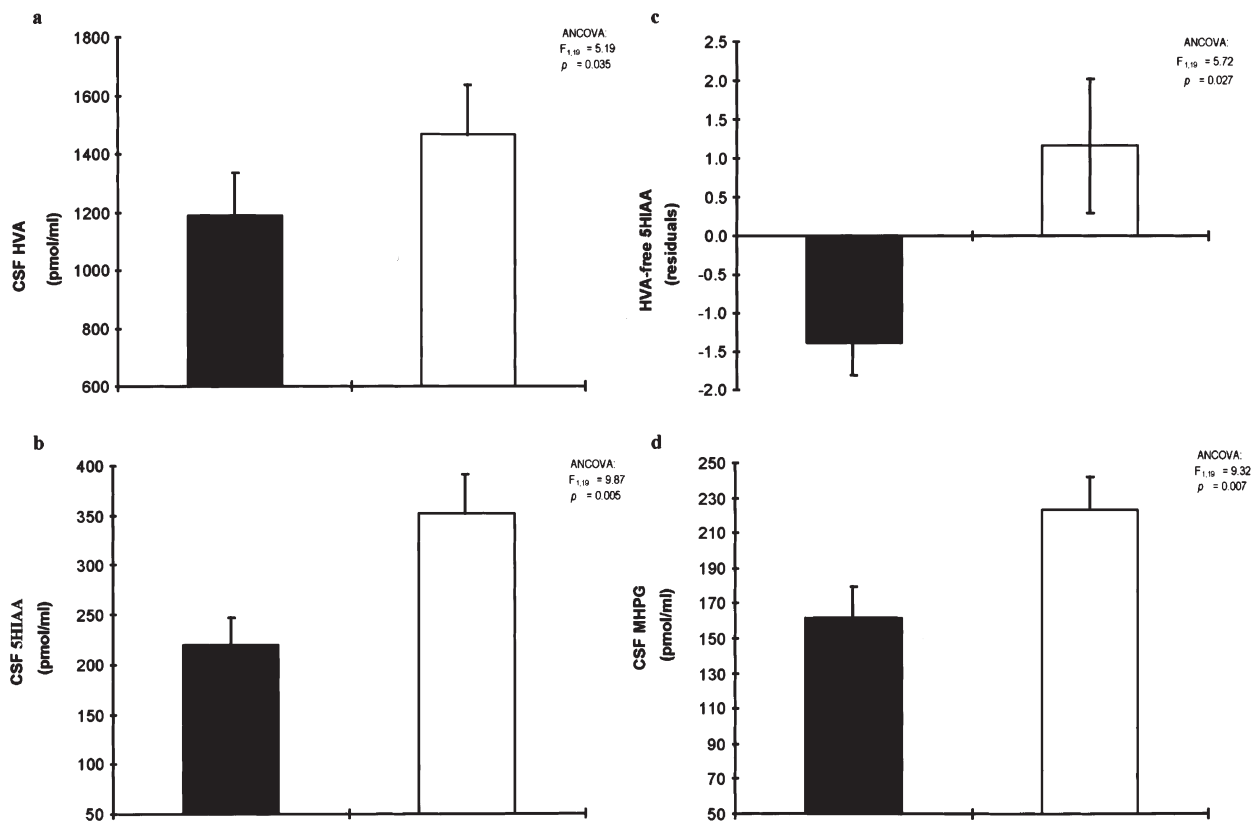


Figure 1. Mean values of CSF monoamine metabolites [(a): HVA; (b): 5-HIAA; (c): residual values of 5-HIAA; and (d): MHPG] among males from groups F (■, $n = 10$ anubis) and H (□, $n = 11$ hybrid); groups compared by analysis of covariance with age in months as the covariate.

Southwest Foundation for Biomedical Research produced a mean MHPG value (83 ± 31 pmol/ml) closer to that of similarly housed cynomolgus macaques than to values seen either in free-ranging rhesus or in ANP baboons. Furthermore, others have reported “unexplained” variability in MHPG (but not HVA or 5-HIAA) among rhesus monkeys housed in different geographic locations (Shelton et al. 1988). It is thus possible that environmental factors such as stress influence MHPG concentrations to a greater extent than those of the other monoaminergic metabolites. In fact, there is evidence from both nonhuman primates and rodents indicating that acute stress causes an increase in sympathetic activity that appears to be associated with an increase in brain and CSF MHPG (e.g., Hellriegel and D’Mello 1997; Higley, Suomi and Linnoila 1991).

A third set of findings concerned the relationships among the monoamine metabolites and between the metabolites and age. As in previous work, the present study found relatively high correlations among the monoamines, particularly between HVA and 5-HIAA (Raleigh et al. 1983; Kaplan et al. 1995; Mehlman et al. 1994). Significant correlations between these metabolites and MHPG have been seen previously in our laboratory (Kaplan et al. 1994; Kaplan et al. 1995) but gener-

ally have not been reported by others (Mehlman et al. 1994). In fact, the current data set contains an unusually high correlation between MHPG and each of the other metabolites. One possibility for the level of correlation observed in this study is that the monoamine oxidase (MAO) functional reserve may be less in wild baboons than in captive animals, and therefore have a substantially greater influence in regulating the monoamines. With respect to this possibility, data from African green monkeys (*Cercopithecus aethiops*) and two Asian macaques suggest there is relatively little variation in brain MAO across species (Riachi and Harik 1992). Alternatively, in wild animals, there could be a higher correlation in neuronal activity across these three related neurotransmitter systems. Finally, the high correlation could represent a chance finding in this relatively small population. Data collections in progress from wild baboons should help resolve this issue.

The current data also revealed an inverse relationship between all of the metabolite concentrations and age, though it was statistically significant only for HVA. The literature relating age to monoamine concentrations is often difficult to interpret due to constricted age ranges, mixed cross-sectional and longitudinal data, and (among humans) the frequent use of popula-

tions compromised by illness (e.g., monkeys: Raleigh et al. 1992; Higley et al. 1991; Shelton et al. 1988; human beings: Bowers and Gerbode 1968; Kruesi et al. 1988; Seifert et al. 1980; Tohgi et al. 1993). Nonetheless, a decline in HVA with age has been consistently observed in macaque populations (Shelton et al. 1988; Higley et al. 1991). There is one report indicating that MHPG declines with age in monkeys (Shelton et al. 1988), and conflicting reports concerning age-associated change in 5-HIAA (Raleigh et al. 1992; Higley et al. 1991; Shelton et al. 1988). The results from the present set of wild baboons are convincing regarding an age effect on HVA but are indeterminate with respect to MHPG and 5-HIAA.

Finally, there was significantly greater monoaminergic activity in the hybrid male baboons than in their anubis counterparts, as indicated by higher concentrations of all three metabolites. The high correlation among them makes this outcome somewhat difficult to interpret. As indicated above, the differences between the two groups of baboons could reflect the influence of MAO activity. The 5-HIAA residuals, however, were also relatively high in hybrid males, despite being uncorrelated with either MHPG or HVA. The latter outcome suggests that there may have been a specific serotonergic difference between the anubis and the hybrids, as initially predicted. If this interpretation is correct, the difference between "pure" anubis and hybrids whose anubis ancestry is tempered with hamadryas admixture is consistent with behavioral differences between the two parental forms (Nagel 1973; Nystrom 1992). This conclusion is necessarily constrained by the relatively small sample size and the lack of data from unhybridized hamadryas populations. Furthermore, monoamine metabolite concentrations represent only an indirect index of central monoaminergic activity. In addition, the data do not resolve the question of causality; behavioral differences between the baboon types could arise ontogenetically for undetermined reasons, with the monoamines changing in response to behavior. Nevertheless, in our view, the data reported here provide intriguing initial evidence that taxonomically relevant differences in nonhuman primate social behavior may reflect underlying divergence in neurochemical activity.

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