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CSF Monoamines, Age and Impulsivity in Wild Grivet Monkeys (*Cercopithecus aethiops aethiops*)

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Key Words

Primates · *Cercopithecus aethiops* · Serotonin · Dopamine · Norepinephrine · Adolescence · Impulsivity · Cerebrospinal fluid · Monoamine metabolites

Abstract

Brain monoaminergic activity has been associated with behaviors, such as impulsive risk-taking, that tend to peak during adolescence in humans and nonhuman primates. This study was designed to assess natural variation in monoamine neurotransmitter metabolism in relation to age and behavioral impulsivity in grivet monkeys (*Cercopithecus aethiops aethiops*) living in their native habitat and subject to natural ecological pressures. Cisternal cerebrospinal fluid, collected from 22 animals living in the Awash National Park, Ethiopia, was assayed for the major metabolites of serotonin (5-hydroxyindoleacetic acid, 5-HIAA), dopamine (homovanillic acid, HVA) and norepinephrine (3-methoxy-4-hydroxyphenylglycol, MHPG). Concentrations of HVA declined significantly from one year of age to older adulthood. Further, a significant curvilinear relationship was identified between

age and the 5-HIAA/HVA ratio, with the trough coinciding with the period of adolescence. Finally, behavioral impulsivity, as measured by re-entering baited traps a second time after the animal had already been captured and sampled for CSF, was related to lower levels of MHPG. The results suggest that normal variation in central monoaminergic activity may have functional consequences in wild populations.

Introduction

Central monoaminergic activity, as measured by the concentrations of the major metabolites of serotonin, dopamine and norepinephrine in cerebrospinal fluid, varies through the life cycle in humans and nonhuman primates. Levels of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), and the dopamine metabolite, homovanillic acid (HVA), decline from infancy through the juvenile period to adolescence in captive rhesus monkeys (*Macaca mulatta*) [Kraemer et al., 1989; Higley et al., 1991]. This decline coincides with the developmental reduction in synaptic density from shortly after birth to puberty for serotonergic and

dopaminergic neurons. HVA concentrations continue to decline with age in adult rhesus monkeys [Shelton et al., 1988]. In captive vervet monkeys (*Cercopithecus aethiops sabaues*), CSF 5-HIAA increases with age for adult females, and the ratio of 5-HIAA/HVA increases from adolescence to late adulthood for both males and females [Raleigh et al., 1992]. Although none of the published results include the full age range from infancy through old age, collectively they suggest that the lowest levels of 5-HIAA, and 5-HIAA relative to HVA, should coincide with adolescence.

Behavioral characteristics that are typical of the adolescent period have also been related to variation in monoaminergic neurotransmitter activity. In many nonhuman primate species, males emigrate from their natal groups at adolescence, and both male and female monkeys actively enter into competitive aggressive interactions to establish their place in the adult dominance hierarchy [Pusey and Packer, 1987; Walters and Seyfarth, 1987]. There is evidence that age of emigration for male rhesus monkeys is influenced by serotonin activity, with the first animals to leave the natal group having the lowest CSF 5-HIAA levels [Kaplan et al., 1995; Mehlman et al., 1995]. Low CSF 5-HIAA in male macaques is also associated with impulsive aggressiveness and a greater tendency to take physical risks [Higley et al., 1992; Botchin et al., 1993; Mehlman et al., 1994; Kaplan et al., 1994; Higley et al., 1996]. Other hallmarks of adolescence, such as exploration, sexual behavior and addictive behaviors, are increased by pharmacological agents that enhance dopamine activity [Pedersen and Prange, 1987; Le Moal and Simon, 1991; Di Chiara, 1995]. Thus dopamine tends to facilitate behaviors typical of adolescence while serotonin provides inhibitory controls [Soubrie, 1986; Depue, 1995; Geraciotti et al., 1998]. These behavioral effects are consistent with the expectation that serotonergic activity, and the ratio of serotonin to dopamine activity, should be relatively low during adolescence.

In the animal and human literature, all three of the monoaminergic neurotransmitter systems have been implicated in impulsivity and sensation seeking [Faustman et al., 1991; Linnoila et al., 1993; Netter et al., 1996; Zuckerman, 1996; Manuck et al., 1998]. The dopamine system is related to impulsivity through activation of reward seeking, sexual and addictive behavior [Cloninger, 1987; Zuckerman, 1995; Depue et al., 1994]. Low serotonin activity is linked to increases in impulsive behavior through reduction in the inhibitory effects of serotonergic neurons on behavioral activating systems [Soubrie, 1986; Meltzer and Lowy, 1987]. Finally, the noradrenergic neurotransmitter system is associated with impulsivity through its role in arousal and

regulation of adrenal activity through the hypothalamic-pituitary-adrenal axis [Siever, 1987]. Concentrations of the noradrenergic metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) are higher in rhesus monkeys reared under conditions promoting heightened reactivity to novelty [Suomi, 1987; Higley et al., 1991; Clarke et al., 1996], and noradrenergic activity is lower in people who are high in sensation seeking [Ballenger et al., 1983].

Here we report the results of one of the few studies to measure natural variation in CSF monoamine metabolites in relationship to behavioral and life history variables in a vertebrate species living in its native habitat and subject to natural ecological pressures [Matter et al., 1998; Kaplan et al., 1999]. The subjects were grivet monkeys (*Cercopithecus aethiops aethiops*) living in the Awash National Park, Ethiopia. Individual differences in neurotransmitter activity are evaluated in relation to age and a measure of behavioral impulsivity [Higley et al., 1996]. The eventual objective of this research is to identify the functional consequences associated with variation in monoamine profiles in monkeys subjected to species-typical ecological pressures.

Materials and Methods

The twenty-two subjects comprising this study were drawn from a single group of grivets inhabiting the Awash National Park, about 200 km east of Addis Ababa, Ethiopia [Phillips-Conroy et al., 1994]. It should be noted that grivets, vervets, and African green monkeys are subspecies of *Cercopithecus aethiops*, a superspecies that is native to much of sub-Saharan Africa and is naturalized in Barbados and St. Kitts-Nevis in the Caribbean. Like many other old world monkeys, females of this species reside in their birth groups for life while males typically leave their groups around the time of puberty [Cheney and Seyfarth, 1983]. Females reach adolescence at approximately 3–4 years of age and males at 4–5 [Fairbanks and McGuire, 1984; Cheney et al., 1988].

The study group, numbering about 60 individuals of both sexes and all ages, inhabits the riparian woodland and bush along the Awash River. Half of the subject animals had been previously captured for a blood sample for genetic and biomedical investigations in prior years [Jolly et al., 1977; Phillips-Conroy et al., 1994; Jolly et al., 1996]. Other human influence is limited to minimal provisioning due to the monkeys' pilfering food from a campsite situated within their home range. They are not subject to hunting or other direct interference from humans.

Trapping and Assessment of Age

Animals were captured in simple drop traps which were set out on 5 days in a one-week period in June, shortly after the birth season. The traps consisted of soft wire stretched over a square wooden frame, baited with dried maize or fruit, and propped up with a pole [Brett et al., 1982]. The monkeys were tranquilized immediately after capture with ketamine hydrochloride (i.m. approximately 10 mg/kg body weight) administered by hand syringe. Each tranquilized animal was examined, weighed, measured and palm-printed (for identification). In addi-

tion, each animal was injected with an electronic chip (Trovan) for long-term identification and given a unique shave mark for short-term, distant identification.

The eruption status of each tooth was recorded in the field, and a dental cast made of the maxilla using alginate as impression material and dental stone for casting. Although captive animals generally erupt teeth at a younger age than do their relatives in the wild [Phillips-Conroy and Jolly, 1988], in the absence of direct knowledge of individual ages of the Awash grivets, we estimated ages for immature animals from tooth eruption patterns of vervets (*C. a. sabaues*) of known age from the UCLA/VA Nonhuman Primate Research Facility at Sepulveda, California [Fairbanks, 1993]. Adolescent males (age 4–5) were also identified by the development of species-typical blue scrotal coloration. For animals with completed dentition, the tooth casts were examined for their degree of occlusal wear, and adults were grouped into two categories: prime (from 6–9 years of age) and old (>10 years). The 22 subjects included 14 males and 8 females and were aged as follows: 3 one year olds, 4 two year olds, 3 three year olds, 2 four year olds, 2 five year olds, 4 prime adults and 4 old adults. Animals ranged in weight from 1.1 kg for the smallest yearling to an average of 3.0 kg for adult females and 4.4 kg for adult males. Average body mass index was 25 for adult females and 29 for adult males.

Collection and Preservation of CSF

Collection of CSF is described in detail in Kaplan et al. [1999]. Briefly, the animal to be sampled was placed on its right side with the head flexed, the hair at the nape of the neck was shaved, and 1 ml of CSF was drawn from the cisterna magna with a 25 gauge needle. The sample was ejected into a polypropylene vial containing 100 ng glutathione. The vials were placed in a wet cloth bag and allowed to cool by evaporation. Four to eight hours later they were placed in liquid nitrogen and remained frozen until assay. Prior testing of the effects of storage of CSF for up to eight hours at ambient temperature in this manner indicated that this procedure does not cause significant degradation of the metabolite concentrations [Kaplan et al., 1999].

The length of time under ketamine anesthesia prior to CSF sampling varied across animals and was longest for monkeys captured on the first day of trapping. Comparison of metabolite concentrations by trapping day or by estimated time under ketamine, however, indicated that these variables had no systematic effects on metabolite levels in this study.

Assessment of Monoamine Metabolites in CSF

Samples were coded and run together in a single set of consecutive runs. In this laboratory the inter-assay coefficient of variance is less than 5% for CSF metabolite assays repeated five times over a period of four months. An aliquot of each sample was mixed with an equal volume of cold mobile phase, filtered by centrifugation (6,000 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 (HPLC) with electrochemical detection, according to the method of Scheinen et al. [1983]. This allows simultaneous evaluation of the three major monoaminergic metabolites in CSF: (1) 3-methoxy-4-hydroxyphenylglycol (MHPG), the norepinephrine metabolite; (2) 5-hydroxyindoleacetic acid (5-HIAA), the serotonin metabolite; and (3) homovanillic acid (HVA), the dopamine metabolite.

Field Measurement of Impulsivity

Several animals that had been captured and sampled on one trapping day, re-entered the traps and were recaptured on one or more of

Table 1. Descriptive statistics and correlations among monoamine metabolite levels (pmol/ml)

Metabolite	N	Mean	SD	Min	Max	Pearson r	
						HVA	MHPG
5-HIAA	22	330	74	199	500	0.71**	0.34
HVA	22	1,431	305	901	1,928		0.52*
MHPG	22	227	57	148	398		

* $p < 0.05$; ** $p < 0.01$.

the remaining trapping days, 2 to 7 days later. Recaptured animals were identified by the distinctive shave at the nape of the neck made for CSF sampling, and the unique identification code emitted by the Trovan chip. One animal that had lost its chip was identified by comparing its palm prints with those of animals of the same age-sex class that were sampled for CSF on one of the prior trapping days. Recaptured animals are considered to be less cautious and more impulsive than animals that avoided the traps on the future encounters [Higley et al., 1996]. Animals captured for the first time on the last two days of trapping were excluded from this assessment, because they had less opportunity to be re-trapped.

Results

The mean value, standard deviation, maximum and minimum value for each metabolite, and correlations among the three measures are shown in table 1. Concentrations of HVA were positively correlated with both 5-HIAA ($r = 0.71$, $p < 0.01$) and MHPG ($r = 0.52$, $p < 0.05$). Levels of 5-HIAA and HVA were in the range of values that have been reported in the literature for CSF samples of vervets (*Cercopithecus aethiops sabaues*) taken under controlled captive conditions [Raleigh et al., 1992]. The MHPG levels were higher than those typically reported for macaques and captive baboons, but in the same range as those found for baboons at the Awash National Park [Kaplan et al., 1999].

Age

Based on prior reports, we expected concentrations of HVA to decline with age throughout the life span. We also expected 5-HIAA and the ratio of 5-HIAA/HVA to show a curvilinear relationship to age, with the lowest values coinciding with adolescence. The results from the field sample were consistent with two of these three predictions. Levels of HVA declined significantly with age throughout the life span, from one year through older adulthood ($r = -0.44$, $n = 22$, $p < 0.05$). The effect of age on 5-HIAA was not statisti-

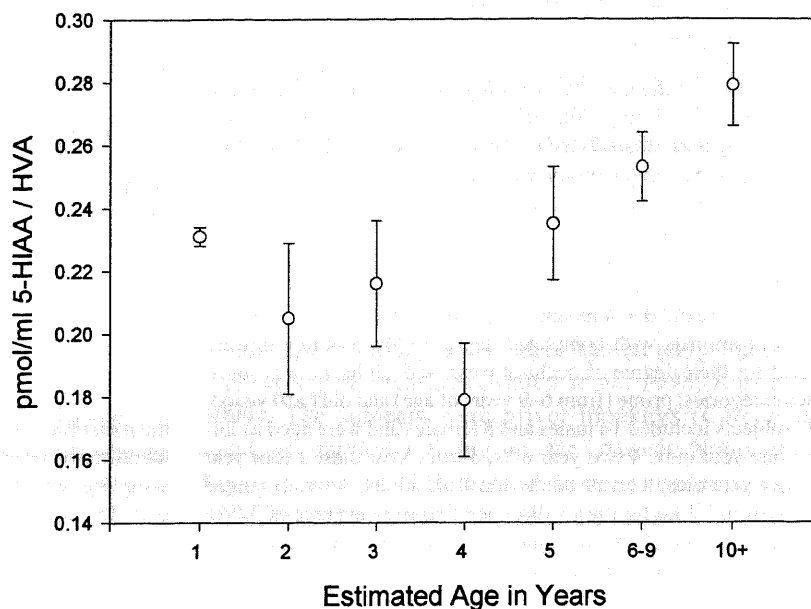


Fig. 1. Mean (\pm standard error) for ratio of 5-HIAA/HVA by age class for wild grivet monkeys.

cally significant in this sample. However, the prediction that the ratio of 5-HIAA/HVA would decline from birth to adolescence and then rise through adulthood was confirmed. A regression analysis demonstrated significant linear and quadratic contributions of age to predicting the 5-HIAA/HVA ratio (Linear $F = 7.87$, $p = 0.01$; Quadratic $F = 8.93$, $p < 0.01$). This effect is illustrated in figure 1. The lowest values of 5-HIAA/HVA were for a 3-year-old female and a 4-year-old male.

This sample was not large enough to evaluate age effects separately for males and females, but there were no significant effects of sex for any of the four measures. Partialling out sex in the above relationships did not alter any of the results (age \times HVA: partial $r = -0.44$, $p < 0.05$; curvilinear regression model of age by 5-HIAA/HVA ratio, controlling for sex: $F = 6.04$, $p < 0.01$).

Impulsivity

Of the 17 animals originally captured prior to the last two days of trapping, 7 were recaptured one or more times. Re-trapping was most common for juvenile males, but females and adult males also re-entered the traps. Figure 2 shows the values of the three monoamine metabolites for the 7 animals who were recaptured and 10 who were not. The means (\pm SE) for 5-HIAA (Recaptured: Yes = 336 ± 28 ; No = 328 ± 28) and HVA (Recaptured: Yes = $1,506 \pm 107$; No =

$1,473 \pm 101$) were not significantly different. There was a significant relationship between levels of MHPG and re-trapping. Re-trapped animals had lower levels of MHPG (Yes = 205 ± 7 ; No = 263 ± 21 ; t , unequal variances = 2.7, $df = 11.1$, $p < 0.05$).

The group of recaptured animals was younger, on average, than the animals that were not re-trapped. Matching animals for age in the analysis, however, did not alter the result (MHPG mean difference = 44.9, matched $t = 2.2$, $df = 12$, $p < 0.05$). Similarly, controlling for sex in a 2×2 analysis of variance did not change the relationship between re-trapping and MHPG ($F = 5.06$, $df = 1, 14$, $p < 0.05$).

Discussion

The results from this report, along with those of an associated study of baboons in the anubis/hamadryas hybrid zone [Kaplan et al., 1999], support the feasibility of measuring neurotransmitter metabolites in nonhuman primates in their native habitat. Average values of serotonin and dopamine metabolites and changes in metabolite concentrations with age were comparable to those that have been reported in age restricted samples of vervets and macaques in captivity [Higley et al., 1991; Raleigh et al., 1992; Kaplan et al., 1994]. Even with limitations of sample size and time to

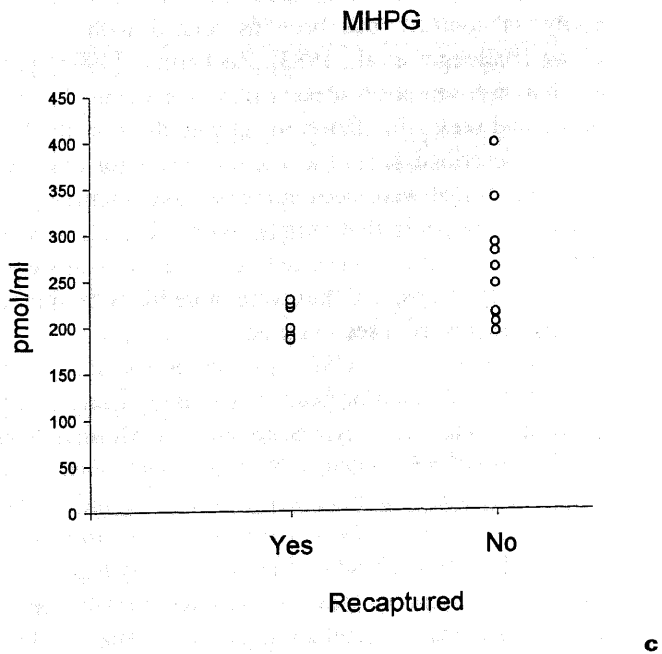
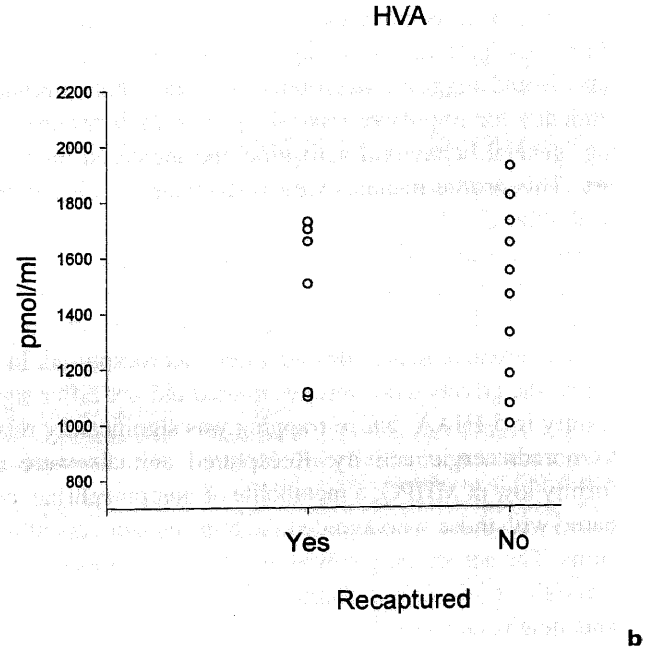
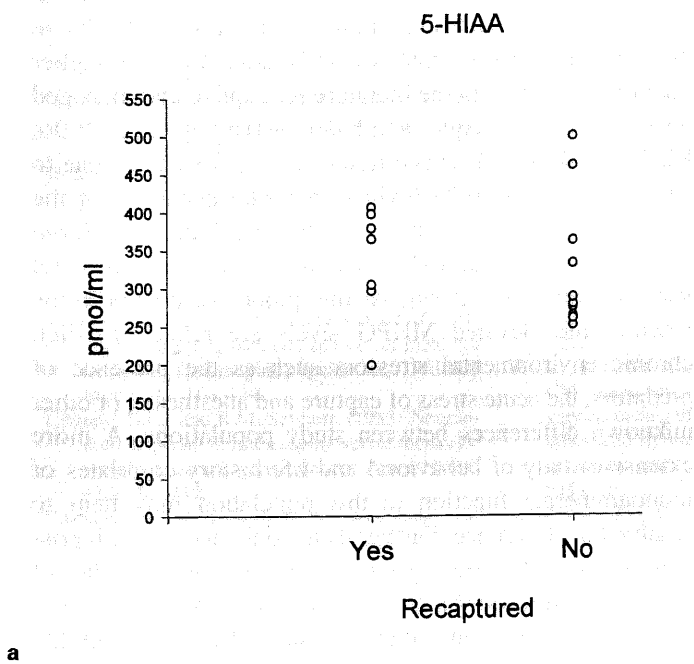


Fig. 2. Concentration in pmol/ml of (a) 5-HIAA, (b) HVA and (c) MHPG by measure of impulsivity.

assess individual differences in behavior, this study was able to identify statistically significant relationships between monoamine metabolites, age and a measure of impulsivity.

This study of free-ranging grivet monkeys found a significant curvilinear relationship between age and the 5-HIAA/HVA ratio, with the trough coinciding with the period of adolescence (ages 3–4 for females, 4–5 for males). Studies focusing on the adolescent age period for male monkeys have found evidence that low serotonergic activity is related to risk-taking behavior (taking longer leaps between branches), injudicious aggression (measured by the presence of bite wounds, the percentage of aggression that involves contact, and increased mortality), and early emigration from the natal troop [Kaplan et al., 1994; Mehlman et al., 1994, 1995; Higley et al., 1996]. Behaviors related to dopamine neurotransmission also pertain to the adolescent age period. The dopamine system is believed to play a strong role in the activation and facilitation of reward-seeking behavior [Depue, 1995], and dopamine agonists increase sexual motivation and performance, locomotion, exploratory behavior and aggression [Everitt, 1979; Le Moal and Simon, 1991; Kalivas and Barnes, 1993]. Moreover, there are numerous interactions between the serotonergic and dopaminergic pathways in mammalian nervous systems, with serotonin providing an inhibitory influence over dopamine modulated facilitatory effects on behavior [Depue,

1995; Geraciotti et al., 1998]. The 5-HIAA to HVA ratio is, therefore, a measure of the relationship between two interacting and partially opposing systems. Low values of this ratio would suggest a neurobiological state that combines a tendency for impulsive risk-taking with high reward-seeking, general behavioral activation and increased interest in sex. This profile matches well with changes in behavior at adolescence.

Higley et al. [1996] used repeated captures as an index of risk-taking in free-ranging rhesus monkeys, and found that recaptured males had lower CSF 5-HIAA and were rated as more aggressive than males who were not recaptured. In this study, the grivets who were recaptured did not differ significantly in 5-HIAA, but re-trapping was significantly related to noradrenergic activity. Recaptured animals were uniformly low in MHPG, a metabolite of norepinephrine, compared with those who avoided the traps on subsequent occasions. The noradrenergic system is typically associated with activation of the hypothalamic-pituitary-adrenocortical axis, and heightened noradrenergic activity has been related to fearfulness and anxiety [Uhde et al., 1984]. In rhesus monkeys, levels of CSF MHPG are increased by stressful early rearing conditions that lead to greater behavioral and physiological reactivity to novelty [Suomi, 1987; Higley et al., 1991; Clarke et al., 1996]. Relatively low noradrenergic activity, in contrast, has been associated with sensation seeking [Ballenger et al., 1983]. Zuckerman [1995] postulates that high sensation seekers may be chronically under-aroused and seek stimulation to activate the system. In the situation described here, the traps baited with corn were novel stimuli that were both attractive and potentially dangerous. It is possible that animals with relatively low noradrenergic activity experienced less fear and anxiety in response to the traps, and thus were more likely to approach and seek the reward a second time.

Previous studies of CSF monoamine metabolites and behavior of nonhuman primates from large managed island populations, such as Cayo Santiago and Morgan Island, have identified relationships between metabolites levels, aggression, risk-taking, inter-group movement and mortality rates [Kaplan et al., 1994; Mehlman et al., 1994, 1995; Higley et al., 1996]. These settings share many features with natural populations, but they also have a higher than normal density which may exacerbate aggressive behavior. Provisioning minimizes the influence of dietary variation on behavior and brain function, and the lack of predators removes an important source of behavior-related mortality. The results reported here are generally consistent with prior studies and also support the feasibility of collecting meaningful data on neurotransmitter systems of a wild primate in

its native habitat. We did find one substantial difference in monoamine concentrations, however. Levels of MHPG in this sample of grivets from Awash National Park are higher than those reported in the literature for captive and managed populations of macaques and baboons [Higley et al., 1996; Kaplan et al., 1999]. This difference is unlikely to be due to species or size, as the MHPG values for the grivets are in the same range as those obtained for wild baboons (*Papio hamadryas anubis* and *P. h. hamadryas*) at the same field site [Kaplan et al., 1999]. At this point, we do not know whether the elevated MHPG levels are related to diet, chronic environmental stressors such as the presence of predators, the acute stress of capture and anesthesia, or other unknown differences between study populations. A more extensive study of behavioral and life history correlates of monoaminergic function in this population may help to resolve this difference. Further data would also make it possible to begin to measure the fitness costs and benefits of enhanced and reduced activity in these systems. This type of information would contribute to our understanding of the evolution of the monoaminergic systems. Moreover, a clearer picture of the functional consequences of normal variation in monoaminergic activity in natural ecosystems would aid in interpreting the role of these systems in behavioral dysfunction.

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