URIC ACID IN NONHUMAN PRIMATES WITH SPECIAL REFERENCE TO ITS RENAL TRANSPORT

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INTRODUCTION

This review is limited to renal uric acid transport and to any ancillary data on plasma or urinary urate concentrations and uricase in nonhuman primates only. Recently a very comprehensive review on renal mechanisms for the regulation of uric acid excretion in man and numerous other species has been published (1); this excellent review should be consulted by all individuals interested in uric acid. Older reviews that briefly touch upon urate metabolism in nonhuman primates have also appeared (2, 3).

There has been considerable confusion in the literature in which nonhuman primates have been utilized as experimental subjects because the word monkey was usually used in the materials section without regard to genus, species, or sex. However, this unfortunate situation is improving. All primates are mammals but not all mammals are primates. Man is the highest primate; the nonhuman primates comprise the Old and New World monkeys, the anthropoids or great apes (chimpanzee, orangutan, gorilla), and the lesser apes (gibbon and siamang). It is to be stressed that an ape is not a monkey. Excellent volumes on the classification of living primates are available (4, 4a).

In previous years the increased demand for nonhuman primates in biomedical research has precipitated a dangerous and alarming depletion of these animals in their natural habitat to the point that some are now classified as endangered and vanishing species. Therefore, the use of nonhuman primates must not be indiscriminate; wherever possible, they should not be used for terminal studies. In the interests of conservation, there should be a provision for propagation of the species. The Regional Primate Research Centers in the United States and several other institutions are actively engaged in breeding programs.

Because there is a paucity of renal urate studies in nonhuman primates recorded in the literature, we have attempted to be as complete as possible and have included all known references, even those remotely concerning urate. A comprehensive tabulation of uric acid values in plasma and urine has been made available by the Primate Information Center of the Regional Primate Research Center at the University of Washington (5).

ENDOGENOUS PLASMA OR SERUM URATE IN NONHUMAN PRIMATES

Old World Species

All Old World (Africa, Asia, Far East) monkeys have extremely low circulating serum urates. An early report of blood uric acid in a "monkey" (presumably a rhesus) was 0.4 mg/100 ml (6).

Macacca mulatta, the well-known rhesus, possess endogenous urate levels in males and females of 0.28–0.65 mg/100 ml (7), and the following mean values: 0.35 mg/100 ml (8), 0.88 mg/100 ml (9), 0.3 mg/100 ml (10, 11). Doloway et al (12) reported a plasma urate range of 0.9–1.4 mg/100 ml in female rhesus monkeys. Species other than the rhesus such as the stump-tailed macaque (*M. arctoides*) have a plasma urate less than 0.5 mg/100 ml (13) and 0.3 mg/100 ml (10, 11); the crab-eating monkey (*M. fasicularis*) was 0.5 mg/100 ml (10, 11). Recently Tisher, Schrier & McNeil (11a) listed values for mean serum uric acids of 0.5, 0.7, and 0.7 mg/100 ml for the rhesus, crab-eating macaque, and stump-tailed macaque, respectively. Similarly another species of macaque, the male Celebes black ape (*Cynopithecus niger*), had a plasma urate less than 0.5 mg/100 ml (13). A group of monkeys closely related to the macaques, i.e. the baboons of Africa, have been reported to possess no detectable serum uric acid by the uricase method (14). Using a colorimetric method, de la Pena, Matthijssen & Goldzieher (15) presented plasma urate values from *Papio* sp. with a mean of 0.7 and a range of 0.1–1.6 mg/100 ml; the male olive baboon (*P. anubis*) has a plasma urate less than 0.5 mg/100 ml (13). Weber et al (16) found mean plasma urates of 0.4 mg/100 ml in the chacma baboon of South Africa (*P. ursinus*) whereas Murphy et al (17) gave a mean figure of 0.21 for this species. Mean values for the yellow baboon (*P. cynocephalus*) of 0.4 mg/100 ml have been recorded (10, 11). One study in the Guinea baboon (*Papio papio*) (18) reported much higher values of 3.35 (range 2.13–5.43) mg/100 ml for randomly sexed mature animals. This large difference from other reported values for the baboon remains unexplained. Serum uric acid values for the Gelada baboon (*Theropithecus gelada*) were 1.2 mg/100 ml (K. F. Burns, personal communication). In the male Mandrill (*Mandrillus sphinx*) and the male African green monkey (*Cercopithecus aethiops*), endogenous plasma urate was less than 0.5 mg/100 ml (13); the patas monkey (*Erythrocebus patas*) has a plasma urate of about 0.2 mg/100 ml (unpublished observations). A prosimian, the male thick-tailed bushbaby (*Galago crassicaudatus*), possessed a mean plasma urate concentration of 0.5 mg/100 ml (13). In another primitive prosimian, the tree shrew (*Tupaia glis*), a serum urate concentration of 0.5 mg/100 ml was reported (10, 11); unpublished

observations from our laboratory for endogenous plasma urate in this species were less than 0.5 mg/100 ml.

New World Species

New World (South America) monkeys with the exception of the *Cebus* (10, 11, 13, 19–25) and spider (13) and woolly monkeys (D. E. Duggan and R. M. Noll, personal communication) have vanishing low endogenous plasma urates. Endogenous plasma urate in the spider monkey (*Ateles* sp.) was reported to range from 3.3–6.3 mg/100 ml (13), whereas the woolly monkey (*Lagothrix lagothricha*) had a mean plasma urate of 3.2 mg/100 ml (unpublished observation). In another study, mean serum urate in the latter species was 3.1 mg/100 ml (10, 11). *C. capucinus* (males and females) maintain plasma levels within a range of 1.5–6.0 mg/100 ml, whereas *C. albifrons* and *C. apella* have plasma urate of 0.8–6.0 (13, 25) and 1.5–6.0 mg/100 ml (13), respectively. The common squirrel monkey (*Saimiri sciureus*) possesses endogenous urate concentrations of 0.5 mg/100 ml (10, 11) or less (13). Other studies in this species reported plasma urates with a mean of 1.0 mg/100 ml (26) and 1.0 with a range of 0.2–2.1 mg/100 ml (27). In the authors' laboratory, it was found that plasma urate in the howler monkey was 0.3 mg/100 ml (unpublished observations). For the night monkey (*Aotus trivirgatus*), Wellde et al (28) tabulated a mean plasma uric acid level of 0.5 mg/100 ml. In the marmoset family, mean serum urates of 2.7 mg/100 ml (range 0–7.7) for the cottontop pinché (*Saguinus oedipus*) have been reported (29); these same authors also report mean values of 1.8 (range 0.6–3.1 mg/100 ml) for the moustached tamarin (*S. mystax*). These values seem rather high for this primitive family but Christen et al (10, 11) reported serum urates of 2.1 mg/100 ml for *S. oedipus*.

Great Apes

In a study by the United States Air Force (30), serum uric acid in male and female chimpanzees aged 1.5–16 years ranged from 2.7 to 5.8 mg/100 ml with the mean being 4.1. This report represented the first published data of its kind. Subsequently, mean serum urate figures for juvenile and mature chimpanzees of 3.57 and 4.68 mg/100 ml, respectively, appeared (18). The authors' laboratory (13) tabulated plasma urates of 2–5 mg/100 ml in male chimpanzees, but we have since noted endogenous levels of 6 mg/100 ml and higher. Clevenger, Marsh & Perry (31) noted serum urates of 2.2–2.7, 3.0, and 1.9–2.8 mg/100 ml for the gorilla, chimpanzee, and orang, respectively. Mean serum urates of 2.4 mg/100 ml (range 1.6–3.4) have been published for the gorilla (32); the same authors (33) reported mean figures for serum urates of 4.4, 2.8, and 2.7 mg/100 ml for infant, juvenile, and adult orangs, respectively. McClure, Keeling & Guilloud (33a) also recently found a mean serum uric acid value of 3.6 mg/100 ml (range 1.7–9.8) for the chimpanzee.

Lesser Apes

Mean plasma urate from the white-handed gibbon (*Hylobates lar*) was ascertained to range from 2–5 mg/100 ml (13), and in a more extensive study the mean value was 3.0 mg/100 ml (5). Also, a plasma urate of 2.6 mg/100 ml (5) was recorded for a female siamang (*H. syndactylus*).

URICASE: PRESENCE OR ABSENCE AND URIC ACID AND ALLANTOIN EXCRETION

The oxidative enzyme uricase catalyzes the aerobic oxidation of uric acid to the more soluble and readily excretable allantoin (for review see reference 3). The presence of uricase is responsible for the relatively low concentrations of circulating serum urate in most monkeys when compared with man and the great apes who maintain serum levels at much higher concentrations because of the mutational loss of this enzyme during the course of evolution (1). The first report that liver uricase was present in any nonhuman primate came from Wells (34) who confirmed its presence in the rhesus monkey. Subsequently, Wells & Caldwell (35, 36) showed that, like man, the chimpanzee and orang liver was devoid of uricase. They also agreed with the earlier important finding of Wiechowski (37) that the chimpanzee, also like man, excretes uric acid but no allantoin in the urine, whereas monkeys excrete chiefly allantoin. Hunter & Givens (38) showed that allantoin was a true urinary end product in the guenon [classified then as *Cercopithecus callitrichus,* while this species name is not mentioned by Napier & Napier (4) but is noted by Chiarelli (4a) to be *C. aethiops* or the green monkey]; only traces of uric acid were excreted. In a subsequent study by the same authors (39) using the same monkey in which they fed purine bases, allantoin was again confirmed to be the chief urinary end product with the appearance of only small amounts of uric acid. Hunter & Ward (40) put man and the chimpanzee in a class by themselves, characterized by the loss of uricolytic power and the consequent replacement of allantoin by uric acid as an end product of purine metabolism. From the historical point of view the papers by Wells, Hunter, and especially Wiechowski are of much interest. Friedemann (41) found that the orang, like the chimpanzee and man, excreted purines mainly as uric acid.

In an extensive study, Rheinberger (42) found that the orang and especially the chimpanzee excreted more uric acid as a percentage of total nitrogen than for the Old World monkeys studied. She also noted that the capuchin or *Cebus* and spider monkeys eliminated more urinary uric acid, thus presaging more definitive studies to be recounted later in this review. Although it was assumed that *C. albifrons* lacked liver uricase because of the rather high circulating uric acid (21), we found that *C. capucinus, C. albifrons,* and *C. apella* did in fact possess liver uricase but that the activity of the oxidative enzyme was present at a very low level (13). Subsequently Simkin (24, 25) and Simkin, Healey & Smuckler (43) demonstrated that even though uricase activity was present in the liver of *C. albifrons,* the relatively high circulating urate was the result of far higher rates of urate synthesis and destruction (formation of allantoin) than in man. Essentially the same results have been found by Duggan and Noll of these laboratories (unpublished observations). Urate pool sizes, turnover times, and biosynthetic rates have been determined by in vivo kinetic studies in the spider monkey, gibbon, and chimpanzee (44).

Hexose infusions in *C. albifrons* led to a rapid increase in plasma and urinary uric acid (45, 46). Data from these studies indicated a prompt increase in urate pool size and were consistent with an accelerated catabolism of a limited pool of preformed purines.

An editorial on the evolutionary aspects of the loss of uricase and nonhuman primate uricase has also appeared (47).

Uricase Demonstration by Histochemical and Electron Microscopic Techniques

Using morphologic techniques alone, Hruban & Swift (48) showed that there was a resemblance between the crystalloid of hepatic microbodies and uricase crystals. Histochemically, de la Iglesia, Porta & Hartroft (49) demonstrated uricase activity in hepatic microbodies of squirrel monkeys (*S. sciureus*). Shnitka (50), although presenting no direct evidence of uricase in hepatic microbodies in nonhuman primates, has presented an interesting account of interspecies differences in these subcellular structures. An excellent review by de la Iglesia (51) on comparative analysis of these hepatic microbodies has appeared in which he showed that *Cebus* and squirrel monkey possess uricase. Tisher et al (52) found that renal microbodies in the rhesus monkey did not contain detectable uricase activity, thus confirming earlier work (34) in which no uricase activity was detected in the kidney. Nakajima & Bourne (53) demonstrated hepatic uricase activity histochemically in various nonhuman primates; they also found no uricase in the kidneys of the chimpanzee, orang, rhesus, and Java monkey (*M. irus*). Hruban & Rechcigl (54, 55) have presented extensive evidence for uricase in monkeys and its absence in the great apes; included is an extensive bibliography on microbodies.

RENAL URATE TRANSPORT

Old World Monkeys

The only study on renal clearances of urate in relation to inulin clearance (C_{ur}/C_{In}) showed that in the species examined, uric acid was avidly secreted by the renal tubules (13) i.e. ($C_{ur}/C_{In} > 1.0$, or urate clearance was greater than the simultaneous inulin clearance (a measure of glomerular filtration rate or GFR). The only exception was that of the thick-tailed bushbaby in which there was limited evidence for net tubular reabsorption of urate ($C_{ur}/C_{In} < 1.0$). In the olive baboon, apparent net urate secretion can be readily inhibited by high doses of *p*-aminohippurate (PAH), probenecid and pyrazinoic acid (unpublished observations). In fact high doses of PAH and probenecid can convert net secretion to net reabsorption giving clearance ratios as low as 0.78 from initial values as high as 2.0 and thus furnishing evidence for bidirectional renal tubular transport of urate. These monkeys were urate loaded by constant intravenous infusion, for they all possess abundant liver uricase and consequently maintain low levels of endogenous urate, the accurate determination of which presents numerous technical difficulties (13). Bidirectional transport of urate is not unique, as it has been demonstrated in various other species (1), but the baboon studies represent the first observance of this general phenomenon in any nonhuman primate.

In slices of kidney cortex in a monkey (presumably a rhesus), Platts & Mudge (56) found that there was no accumulation of uric acid. Cannon, Symchych & DeMartini (57) showed that in antidiuretic *M. mulatta* infused with sodium urate,

there was an increasing urate gradient from renal cortex to medulla with the highest concentration in the papillary tip, whereas in hydrated monkeys, similar infusions were not associated with a urate concentration gradient.

New World Monkeys

In a variety of monkeys, net reabsorption of varying degree was shown (13); C_{ur}/C_{In} from certain members of the family Cebidae varied from about 0.03 representing extensive urate reabsorption to 0.93 (approximately the level of glomerular filtration). The only exception was the red howler monkey in which net secretion was seen ($C_{ur}/C_{In} = 1.8$). The reason for this exception remains unexplained. Unpublished values from this laboratory of C_{ur}/C_{In} for the woolly monkey averaged about 0.13.

In the *Cebus* monkey, Skeith & Healey (21) showed that infusions of probenecid, sulfinpyrazone, and chlorothiazide increased urate clearance whereas β-hydroxybutyrate, lactate, and pyrazinoic acid produced a fall in this parameter. These observations were confirmed and extended to show an apparent tubular maximum (*Tm*) for urate in the *Cebus* that was enhanced by pyrazinoic acid (PZ) and reduced by probenecid (22). Also in this work, it was postulated that high loads of PAH inhibited the secretory moiety for urate by depressing the clearance ratio although not to the degree produced by PZ. Even though net urate secretion could not be demonstrated, the above results strongly suggested that it does exist. Urate was not bound to serum proteins in the *Cebus* (22, 58). May & Weiner (59) reported that *m*-hydroxybenzoic acid (*m*-HBA) was both secreted and reabsorbed by the kidney of *C. albifrons,* both of which processes were "carrier mediated." Also *m*-HBA was a powerful inhibitor of uric acid secretion and a weak inhibitor of PAH secretion; it behaved very much like PZ. Their data suggested that there may be one or more organic anion secretory mechanisms with overlapping specificities. Blanchard et al (60) examined the uricosuric potency of 2-substituted analogs of probenecid in the same species of monkey and found that they were about 10 times as potent as probenecid. Each analog was actively secreted albeit at different rates, and their enhanced uricosuric activity was due to the fact that they are all stronger acids than probenecid. Weiner & Tinker (61) in an extensive study of pyrazinamide and its principal metabolite, the free acid (PZ), conclusively indicated that PZ was bidirectionally transported by active mechanisms in *C. albifrons* in that its clearance was subject to competitive inhibition and insensitive to other manipulations characteristic of passive processes.

In *C. albifrons,* Vinay et al (62–64) ascribed the potent uricosuric action of benziodarone to a stimulation of urate secretion. Recently, Lemieux et al (65), extending their studies with benziodarone in *C. albifrons,* have apparently relinquished their earlier untenable assumption that benziodarone stimulated urate secretion. The marked uricosuric action of benziodarone results from inhibition of urate reabsorption in the proximal tubule in the *Cebus* (66).

Roch-Ramel & Weiner (67, 68), in the only free flow micropuncture studies to date in *C. albifrons,* found that at least 70–80% of urate was reabsorbed in the proximal tubule with no reabsorption of urate detectable in Henle's loop or distal

tubules of surface nephrons. 2-Nitroprobenecid, a uricosuric agent, inhibited net urate reabsorption from the proximal tubule (68).

Known uricosuric drugs in man, with the exception of the potent zoxazolamine, were uricosuric in the *Cebus* (69). Also in the *Cebus,* mercurial diuretics in the absence of PAH loading were only slightly uricosuric; *Tm* for PAH was variably reduced (70).

Great Apes

It has been long recognized that the animals closest to man are the great apes. The chimpanzee (*Pan troglodytes*), however, is most closely related to man both serologically and immunologically (71). Because of wide species differences in the renal handling of urate (1, 72), we undertood a project to study renal urate transport in the chimpanzee systematically. Our very first experiments were carried out through the generous cooperation of the United States Air Force at Holloman AFB, New Mexico. Thereafter, through acquired knowledge and experience, our own small chimpanzee colony was established.

The first published work employing conventional renal clearance techniques in the chimpanzee was that of Smith & Clarke (73), although they did not measure urate clearance. Similarly, Gagnon & Clarke (74) enlarged on these earlier studies (73), but no urate data were presented. In another baseline study (75) of renal function in immature chimpanzees, urate clearances were not performed.

Elmadjian (76) reported that young chimpanzees (18.2 kg) excreted an average of 348 mg of uric acid/day or 0.267 mg/min, but no plasma urate values were given. Gagnon (77), assuming a plasma level of urate of 2 mg/100 ml, calculated that uric acid clearance would be about 13 ml/min or 0.73 ml/kg/min; this value was much greater than was found in an extensive study of urate clearances in adult chimpanzees (78) in which C_{ur}/GFR based on 417 observations was 0.104±0.008. The corresponding figure for C_{ur} was 0.215 ± 0.022 ml/min/kg. Pyrazinoic acid greatly diminished C_{ur}/GFR, the effect of which was not overcome by probenecid (78). Also in this study, the increased urate clearance brought about by probenecid was promptly nullified by pyrazinoic acid. It is also true that all known uricosuric drugs in man are effective

The mercurial diuretics mersalyl (Salyrgan) and chlormerodrin (Neohydrin) markedly reduced Tm_{PAH} (80). Conclusive proof was presented that intravenous mersalyl, in the absence of PAH loading, readily converted net urate reabsorption to unequivocal net secretion; the highest C_{ur}/GFR noted was 1.98 (81). Also in the latter study, certain inhibitors of organic anion secretory transport prevented the appearance of net urate secretion; the magnitude of the uricosuric response correlated fairly closely with the excretion of mercury (81). Pyrazinoate (PZ) was apparently secreted and reabsorbed by active transport processes for the clearance ratio (C_{PZ}/GFR), normally greater than 1.0 was reduced to values well below control by probenecid, PAH, Diodrast, mersalyl, sulfinpyrazone, etc (82); PZ had a dual effect on urate excretion, for at a concentration in plasma of less than 10 μg/ml, there was a concentration related fall in C_{ur}/GFR. This ratio was maximally depressed at plasma PZ concentrations of 10–100 μ/ml. At PZ concentrations greater than

600 μg/ml, a definite uricosuric response was seen. These results were consistent with a model of urate transport in the chimpanzee involving high rates of bidirectional transtubular fluxes (82).

A new hypolipidemic-uricosuric agent, halofenate, was found to be uricosuric in the chimpanzee; halofenate free acid was actively secreted and passively reabsorbed (83) and was thought to act like other uricosuric drugs by partially inhibiting renal tubular reabsorption of urate at the luminal membrane.

A review on the morphology and anatomy of the urinary system in nonhuman primates has also appeared (84).

In summary, we have tried to show that, even among the nonhuman primates, marked species differences do exist regarding plasma urate concentrations, presence or absence of uricase, and the net renal clearance of uric acid. The complexities of urate transport are great, and this is eminently apparent in this specialized animal order. Even the superficial resemblance of the renal handling of urate between the chimpanzee and man can be misleading whenever one endeavors to extrapolate results to man. It is the relationship of the relative affinities (differing susceptibilities) of the urate transport mechanisms to various drugs, including the important area of drug interactions, which contributes to these highly complex renal mechanisms. There is also evidence that the chimpanzee urate transport system is more sensitive to the action of various drugs than is the case for man (Weiner and Fanelli, unpublished observations).[1]

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[1]Since submission of this review, values for serum uric acid from the rhesus monkey of 1.0–1.4 mg/100 ml have been noted (85).

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