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Sex-Dependent Metabolism of Xenobiotics

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Sex-dependent differences in xenobiotic metabolism are most pronounced in rats. Consequently, this species quickly became the most popular animal model to study sexual dimorphisms in xenobiotic metabolism. Exaggerated sex-dependent variations in metabolism by rats may be the result of extensive inbreeding or differential evolution of cytochrome P450 (CYP) isoforms in mammals. Sex-dependent differences in other xenobiotic-metabolizing enzymes such as sulfotransferases, glutathione transferases, and glucuronyltransferases have also been observed. Animal studies are used to help determine the metabolism and toxicity of many chemical agents in an attempt to extrapolate the risk to humans from exposure to these agents. One of the most important concepts to consider in using rodent studies to identify sensitive individuals in the human population is that human CYPs differ from rodent CYPs in both isoform composition and catalytic activities. Metabolism of xenobiotics by male rats can reflect human metabolism when the compound of interest is metabolized by CYP1A or CYP2E because there is strong regulatory conservation of these isoforms between rodents and humans. However, problems can arise when rats are used as animal models to predict the potential for sex-dependent differences in xenobiotic handling in humans. Information from numerous studies has shown that the identification of sex-dependent differences in metabolism by rats does not translate across other animal species or humans. To date, sex-specific isoforms of CYP have not been identified in humans. This lack of expression of sex-dependent isoforms in humans indicates that the male rat is not an accurate model for the prediction of sex-dependent differences in humans. Differences in xenobiotic metabolism among humans are more likely the consequence of intraindividual variations as a result of genetics or environmental exposures rather than being due to sex-dependent differences in enzyme composition.

Sex-Dependent Differences in Metabolism in Rats

Over 50 years ago, female rats were observed to be more sensitive to the effects of barbiturates than male rats. Females showed a prolonged sleep time after exposure to hexobarbital (Holck et al., 1937). Results from early studies designed to examine the mechanism of this sex-dependent difference in response to specific barbiturates demonstrated that females had higher and more prolonged serum concentrations of the parent compound due to a lower rate of metabolism as compared with male rats. Subsequent studies with a variety of chemicals and drugs have shown that, in general, male rats have higher rates of xenobiotic metabolism than females.

In the last 25 years, large advances have been made in the study of xenobiotic metabolism. Detailed experiments have characterized the most important group of xenobiotic-metabolizing enzymes found in mammals, the cytochromes P450 (CYP). CYP isoforms catalyze the oxidation

and reduction of a variety of endogenous compounds such as steroid hormones, fatty acids, and prostaglandins as well as xenobiotics. In general, CYP-mediated reactions facilitate the excretion of xenobiotics. However, reactive metabolites can also be formed via CYP-dependent metabolism. Approximately 40 genes code for specific isoforms in the rat genome (Nelson et al., 1996), with four major subfamilies of CYP isoforms in rat liver exhibiting different but somewhat overlapping substrate specificities.

Female rats have 10-30% less total CYP as compared with male rats. This helps to explain why female rats in general metabolize many drugs and compounds more slowly than male rats. In many instances where a sex-dependent difference in metabolism is observed, there can be a 2- to 20-fold difference in the metabolism of a specific agent, however. This suggests that the isoform or isoforms of CYP that metabolize the chemical are very different between males and females.

There are sex-dependent differences in the expression of microsomal CYP450 isoforms that catalyze the hydroxylation of steroids (Waxman et al., 1985). These differences are developmentally regulated and are manifest in adult animals. Immunological data have shown that CYP2C12 (steroid sulfate 15b&endash;hydroxylase) is in higher concentration in female than in male rat liver. CYP2C12 is female-specific in adults but is present in appreciable levels in immature and old male rats. Isoforms CYP2C7 and CYP2A1 are female-predominant. In contrast, CYP2C11 (microsomal 16-hydroxylase) is male-specific. This isoform is not expressed in females at all but is present in highest concentration in sexually mature males. Studies in castrated males and in females supplemented with testosterone show that CYP2C11 is under the regulatory control of androgens. Male-predominant isoforms are CYP2A2, CYP3A2, and CYP2A1.

Sexual dimorphisms have been observed in the response to inducing agents in rats. Male rats are generally more responsive to the effects of agents that induce specific isoforms of hepatic CYP450 than are female rats. For example, treatment of Sprague-Dawley rats with phenobarbital (1, 3, or 20 mg/kg) for six days resulted in increases in hexobarbital hydroxylase activity and aminopyrine N-demethylation in hepatic microsomes prepared from male, but not female, rats (Shapiro, 1986).

Sex-dependent differences have also been observed in the expression of conjugative enzymes such as sulfotransferases (Mulder, 1986), glutathione S-transferases (Srivastava and Waxman, 1993), and glucuronyltransferases (Zhu et al., 1996). In general, male rats tend to have higher enzyme activities than do females. With some substrates, however, females have higher rates of conjugation than do males.

Hormonal Regulation of Enzyme Expression

Holck et al. (1937) made the seminal observation that anesthesia induced by hexobarbital and pentobarbital was of a much longer duration in female than in male rats. They reported that this sex-dependent difference was not observed in immature rats three to four weeks of age. Castration of male rats increased the time of hexobarbital-induced anesthesia to the duration observed in female rats. Administration of testosterone to intact and ovariectomized females shortened hexobarbital-induced anesthesia. Holck et al. (1937) concluded that the observed

sexual dimorphism in response to certain barbiturates was a result of the action of the male sex hormone testosterone.

A later study conducted by Brodie (1956) showed that plasma levels of pentobarbital decreased more rapidly in male rats than in females. Administration of testosterone to females increased the rate of the removal of pentobarbital from the plasma. Conversely, administration of estradiol to males slowed the removal of pentobarbital from the plasma. Liver microsomes from male rats metabolized hexobarbital faster than microsomes prepared from females. Microsomes prepared from female rats treated with testosterone metabolized hexobarbital at rates that were similar to the rates observed with male rat microsomes. These data indicate an important role for testosterone in the sex differences in barbiturate metabolism in rats.

Table 1 - Drugs and Chemicals Showing Sex-Dependent Differences in Metabolism in Rats

Agent	**Differences**
Cocaine	Males metabolize the agent two times faster than females
Diazepam	Metabolism is greater in males than females
Hexobarbital	Metabolism in females is slower, resulting in higher blood levels and a prolonged sleep time
Indinavir	Males metabolize the agent three times faster than females
Morphine	Metabolism is greater in males than females
Pentobarbital	Metabolism in females is slower, resulting in higher blood levels and a prolonged sleep time
Tolbutamide	Metabolism is greater in males than females

Various studies subsequent to these early, key findings have illustrated that, in general, male rats have a higher rate of xenobiotic metabolism as compared with females (Table 1). For example, many anesthetics and antidepressants are metabolized more rapidly in male rats. This sex-specific difference results in many chemicals and drugs having longer half-lives and slower clearance in female rats (Table 1). The slower metabolism in female rats produces higher tissue concentrations of xenobiotics that may induce target organ toxicity.

Extensive studies conducted in the 1970s through the 1980s showed that specific concentrations of testicular androgens in the neonate imprint the expression of specific isoforms of CYP450 in the adult rat (Gustafsson et al., 1983). This early imprinting is required for males to express the entire complement of male-specific isoforms. The age of the male is important for castration to affect the expression of CYP450 isoforms. Castration of adult males did not reduce enzyme activity to female levels. However, castration of male neonates brought about complete feminization of the isoforms expressed in the adult male liver. Castration caused a decrease in the expression of CYP2C18 and CYP3A2 and an increase in the expression of CYP2C19. Castration did not affect the expression of the male forms of CYP450 when it was done after five weeks of age. Also, the expression of CYP450 isoforms in a castrated neonate was not affected if the animal was supplemented with testosterone on day three after castration. These observations indicate that critical levels of androgens in the male neonate imprint the liver to express the male complement of CYP450 isoforms. In contrast, females are not as dependent on circulating levels

of estradiol for the expression of the female isoforms of CYP450. Ovariectomy of female neonates reduces but does not abolish the expression of CYP2C19 (Table 2).

Table 2 - Effects of Various Treatments on the Expression of Sex-Specific Isoforms of Cytochrome P450 in Rat Liver

Treatment	Males	Females
Steroid administration to intact animals	Estradiol reduces expression of male isoforms.	Testosterone reduces expression of female isoforms, but increases expresion of some male-specific isoforms.
Castration*	Reduces male-specific isoforms.	Reduces female-specific isoforms.
Castration followed by steroid administration	Testosterone increases expression of male isoforms.	Estradiol restores levels of female-specificisoforms.
Hypophysectomy	Significantly reduces the level of male-specificisoforms.	Causes expression of male-specific isoforms.
Hypophysectromy followed by steroid administration	No effect of estradiol.	No effect of testosterone.
Hypophysectomy followed by growth hormoneadministration	Isoform expression reflects pattern of growth hormonesecretion.	Isoform expression reflects pattern of growth hormonesecretion.

*The age of the animal at the time of castration determines the effect on the composition of hepatic cytochrome P450 isoforms. For example, castration does not have an effect if animals are older than five weeks of age.

In addition to androgens, growth hormone, somatostatin, insulin, and thyroxine each play a specific role in the sex-specific expression of CYP450 isoforms in rats. Elegant studies investigating the mechanism of sex-dependent differences in the expression of CYP450 isoforms have demonstrated that regulation of male or female isoforms is at the level of the hypothalamic-pituitary axis. Investigations conducted in the early 1970s (Gustafsson and Stenberg, 1974) demonstrated that hypophysectomy abolished sex-dependent differences in metabolism (Table 2). Xenobiotic metabolism in male rats following hypophysectomy was reduced to the levels seen in females in the 1970s (Gustafsson and Stenberg, 1974). The fact that administration of testosterone did not reverse the effect of hypophysectomy in males indicates that endogenous factors in addition to androgens modulate sexual dimorphism in xenobiotic metabolism.

Subsequent studies showed that the pattern of growth hormone secretion regulates the expression of uniquely male versus uniquely female isoforms of CYP450. The pattern of growth hormone secretion in male and female rats is similar until about the age of 25 days. By 30 days of age, unique patterns of growth hormone secretion develop between male and female rats (Mode et al., 1982). Female rats have constant, low levels of growth hormone with small bursts of secretion (Figure 1). In contrast, males have undetectable levels of growth hormone in the absence of episodic bursts of secretion every 3.5 to 4 hours (Figure 1). The expression of male-specific CYP2C11 is regulated by the pulsitile bursts of growth hormone secretion, while these bursts inhibit the expression of CYP2C12, the female-specific isoform (Legraverend et al., 1992).

Control of the growth hormone secretion pattern in male and female rats is regulated by sex hormones (Mode et al., 1982). In male rats, testosterone stimulates the release of somatostatin, which inhibits the release of growth hormone (Figure 1). This level of regulation at somatostatin is what causes the pulsitile pattern of growth hormone secretion that masculinizes the liver in the expression of CYP450 isoforms. In contrast, secretion of estrogen in female rats stimulates the secretion of growth hormone releasing hormone. Secretion of growth hormone releasing hormone stimulates the release of growth hormone, which results in constant, low levels of growth hormone in female rats (Figure 1). The data suggest that this pattern of regulation of growth hormone secretion by estrogen in the female results in the expression of female-specific isoforms of CYP450 (Figure 1).

An interesting observation in the studies of sex-dependent metabolism is the fact that sex-dependent differences in CYP450 content and monooxygenase activities disappear as rats age (Kamataki et al., 1985). In general, the livers of male rats feminize with regard to CYP450 isoform expression and activities. Enzyme activities in young rats that were much greater in males than in females declined with age in the male and became similar to the activities of a young female (Kamataki et al., 1985). Studies to address the mechanism of the loss of sex-dependent differences in xenobiotic metabolism as rats age have focused on changes in the pattern of growth hormone secretion. As male rats age, the pattern of growth hormone secretion dramatically changes to resemble that of females (Kamataki et al., 1985). Aging male rats no longer show peaks of growth hormone secretion but rather exhibit constant, lower levels of the hormone, as is observed in females (Kamataki et al., 1985).

Sex-Dependent Differences in Other Species

In contrast to the large body of literature detailing the sex-dependent differences in xenobiotic metabolism in rats, less information on this topic exists for other animal species. As molecular biology techniques have improved over the last 10 years, sex-dependent differences in metabolism have been shown to exist in other animals as well. However, the sexual dimorphisms observed in other species are far less exaggerated as compared with the sex-dependent differences observed in the rat.

After the rat, xenobiotic metabolism is best characterized in the mouse. Sex-specific differences in xenobiotic metabolism are observed in certain strains of mice. When a sex-dependent difference in metabolism is observed in rats, male rats always have a higher rate of metabolism than females. When a sex-dependent difference is expressed in mice, however, the difference is dependent on the strain of mouse. Males have higher xenobiotic metabolism in some strains of mice, while females have higher rates of metabolism in other strains (MacLeod et al., 1987). In general, female mice more commonly have higher rates of metabolism than males (MacLeod et al., 1987). Another important difference is that the magnitude of sex-dependent differences is very different in mice as compared with rats. For example, male rats can have an enzyme activity as much as five-fold greater as compared with females. In contrast, when a sex-dependent difference occurs in a specific strain of mouse, the greatest degree of sexual dimorphism is usually about two-fold.

As in rats, serum growth hormone levels and the pattern of growth hormone secretion are the regulatory points for xenobiotic metabolism in mice. However, the pattern of secretion (pulsitile versus constant) appears to have opposite effects on the expression of enzymes in male mice as compared with male rats. Testicular androgens induce hepatic monooxygenases in male rats, while testosterone represses the expression and activity of these enzymes in male mice.

There are fewer studies identifying sex-dependent differences in metabolism in higher animals compared with the amount of work that has been done to address sexual dimorphisms in rats and mice. However, the literature contains information on studies conducted in rabbits, dogs, and monkeys. Sex-dependent differences in xenobiotic metabolism in rabbits occur in the family of flavin-containing monooxygenases, flavo-proteins that oxidize molecules containing nitrogen and sulfur (Tynes and Philpot, 1987). There are examples of sex-dependent differences in metabolism by beagle dogs that appear to be due to differential expression of CYP isoforms (Lin et al., 1996). One study with patas and cynomolgus monkeys did not observe sex differences in metabolism (Jones et al., 1992).

Sex-Dependent Differences in Humans

Progress has been made in identifying the CYP isoforms that are present in human liver (Nelson et al., 1996), with 28 genes identified as coding for this superfamily of enzymes in the human genome. As in rodents, only gene families 1, 2, and 3 are involved in xenobiotic metabolism in humans. However, the major CYP isoform detected in human liver, CYP3A, is in relatively low concentration in rat liver (Table 3). Another key difference is that several CYP450 subfamilies have different substrate specificities in rodent as compared with human liver (Wrighton et al., 1993). For example, human CYP3A has coumarin-7-hydroxylase activity, but none of the isoforms in the rat CYP3A subfamily show significant coumarin-7-hydroxylase activity. Sex-dependent differences have not been reported for any of the isoforms of CYP450 expressed in human liver (Guengerich, 1990).

Table 3 - Comparison of Major Isoforms of Cytochrome P450 in Rodent and Human Liver		
Isoform	**Rodent**	**Human**
CYP1A		
1A1	Present; induced by polycyclic aromatic hydrocarbons.	Present in liver and lung; induced by cigarette smoke.
1A2	Present; induced by polycyclic aromatic hydrocarbons.	Present in liver only; induced by cigarette smoke.
CYP2A		
2A1	Rat testosterone 7α-hydroxylase.	Not present.
2A2	Present.	Not present.
2A3	Present in liver and lung; induced by3-methylcholanthrene.	Not present.
2A4	Mouse testosterone 15α-hydroxylase.	Not present.
2A5	Present.	Coumarin 7-hydroxylase activity; 7-ethoxycoumarin *O*-deethylase activity.
CYP2B		
2B1	Phenobarbital-induced.	Not present.
2B2	Constitutive and phenobarbital-induced.	Not present.
2B6		Gene identified.
CYP2C	Major subfamily in rats; sex-specific isozymes.	Not present.
2C5	Rabbit progesterone 21-hydroxylase.	Not present.
2C8		Retinol metabolism.
2C9/10		Hexobarbital, tolbutamide metabolism.
2C18		Mephenytoin metabolism.
CYP2D		
2D6		Desbrisoquine metabolism.
CYP2E		
2E1	Induced by ethanol, isoniazid, acetone.	Induced by ethanol, isoniazid, acetone.
CYP3A		Major subfamily in adult liver.
3A1	Phenobarbital-inducible.	
3A2	Present in males only; phenobarbital inducible.	
3A3	Present.	
3A3/4		Major isoform in adult liver.
3A5		Higher in adolescent liver.
3A7		Major fetal form; not present in adults.
CYP4A		Small role in metabolism of some fatty acids; induced byclofibrate, ciprofibrate, clofribric acid.

Although the composition and relative proportions of specific CYP isoforms are different in humans and rats, there is strong catalytic and regulatory conservation of the CYP1A1, CYP1A2,

and CYP2E1 subfamilies among the rat isoforms and their human orthologs. Since many chemicals and pharmaceutical agents are metabolized by these isoforms, rats are suitable animal models for investigating the metabolism and toxicity of a wide variety of chemical agents. These enzymes are not expressed in a sex-dependent manner in rat liver.

Most of the information on xenobiotic metabolism in humans has been gathered from clinical studies examining the pharmacokinetics of pharmaceutical agents. Quite often, examining the potential for sex-dependent differences in the handling of a particular xenobiotic was not a primary objective of a study, but both men and women were included in the studies. The pharmacokinetics of many compounds are the same in men and women. However, the pharmacokinetics of some xenobiotics are different in men and women (Table 4).

Table 4 - Xenobiotics Showing Sex-Dependent Differences in Pharmacokinetics in Humans

Agent	**Reported difference**
Acetaminophen	Higher parent plasma concentration in females due to lower glucuronidation
Aspirin	Higher esterase activity in males; lower plasma levels in males.
Chloramphenicol	Higher plasma levels in females.
Chlordiazepoxide	Lower clearance in females as compared with males.
Diazepam	Lower clearance in females as compared with males.
Erythromycin	Higher clearance in females.
Lidocaine	Greater half-life and volume of distribution in females.
Mephobarbital	Greater total body clearance and shorter half-life in young males.
Nortriptyline	Higher metabolism in males; females have higher plasma levels of parent compound.
Oxazepam	Lower clearance levels in females.
Phenytoin	Higher plasma levels in males.
Propranolol	Lower clearance in females due to lower glucuronidation.
Rifampicin	Higher plasma levels in females; higher urinary excretion of parent compound.
Tetracycline	Higher plasma levels in females.

In general, when a sex-dependent difference is observed in humans, females have higher plasma concentrations of the drug as compared with men. These differences have been observed with certain antibiotics, some tricyclic antidepressants, lithium, and aspirin (Giudicelli and Tillement, 1977). A wealth of information is available in the literature regarding sex-dependent differences in benzodiazepam pharmacokinetics in men and women. For example, the distribution of chlordiazepoxide is more extensive in women than in men (MacLeod et al., 1979). Women have a greater distribution of diazepam, which is metabolized by N-demethylation in the liver, than do men. In addition, diazepam clearance is higher in women than in men. Interestingly, the pharmacokinetics of benzodiazepams change in the elderly, with elderly patients showing a reduced clearance and volume of distribution of these drugs as compared with young patients (MacLeod et al., 1979).

Establishing the etiology of sex-dependent differences in drug pharmacokinetics is obviously more difficult in humans than in animals. Potential factors that may contribute to sex-specific differences in the pharmacokinetics of a compound include differences in absorption, bioavailability, distribution, and metabolism. Therefore targeting the contribution of metabolism alone to sex-dependent differences in drug pharmacokinetics in humans is difficult. Differences in the absorption, bioavailability, and distribution of some compounds are related to basic differences in physiology and body composition. For example, the absorption of certain drugs from the gastrointestinal tract may be affected by the fact that both gastric acid secretion and gastric emptying are lower in women as compared with men (Giudicelli and Tillement, 1977). The differences in rates of gastric absorption cause men to achieve peak sodium salicyclate plasma concentrations more quickly than women. Also, the volume of distribution of certain chemicals can be affected by the fact that lean body mass is greater in males, while adipose tissue content is greater in women (Giudicelli and Tillement, 1977). For example, intramuscular injections of drugs are handled differently between men and women because of sex differences in the distribution of gluteal fat. Because of this difference, lipophilic chemicals can have a greater volume of distribution in women as compared with men.

Data from clinical studies indicate that hormonal regulation may play a role in xenobiotic metabolism in humans. There is evidence that the manipulation of normal levels of circulating steroid hormones can alter the way men and women handle xenobiotics. The best examples illustrating the effects of steroid hormones on drug pharmacokinetics come from clinical studies that contain detailed information on oral contraceptive use and menstrual cycle information from female volunteers. For example, there is evidence that the phase of a woman's menstrual cycle can affect the kinetics of a number of xenobiotics by altering drug distribution and clearance. There are changes in gastric emptying rate and acidity of the stomach contents at about day 14 of a 28-day menstrual cycle (MacDonald, 1956). As progesterone rises, ovulation increases the gastric emptying rate and the secretion of acid in the stomach. Therefore the bioavailability of a compound may change depending upon the phase of a woman's menstrual cycle. The phase of the menstrual cycle also has been shown to affect the volume of distribution and half-life of a number of chemicals, including diazepam and acetaminophen (MacLeod et al., 1979).

The data suggest that the hypothalamic-pituitary axis may be the control point for xenobiotic metabolism in humans. The sex difference in the pattern of growth hormone secretion in humans is qualitatively similar to the difference that is observed in rodents (Winer et al., 1990). Growth hormone is secreted in a pulsitile, circadian pattern in both men and women, but women have higher mean growth hormone serum concentrations than men (Winer et al., 1990). The etiology of sex-dependent differences in serum growth hormone levels in humans is not entirely clear.

Although there are sex-dependent differences between men and women in the handling of certain xenobiotics, the differences are not related to differences in CYP isoforms (Guengerich, 1990). Furthermore, the differences in humans are not nearly as distinct as those observed in rodents. In humans, intraindividual differences in metabolism apparently outweigh any differences regulated by sex-specific factors. For example, exposure to inducers of CYP isoforms through either the diet or workplace can produce a profile of hepatic CYP isoforms that may make an individual metabolize a compound differently. Also, genetic polymorphisms in the expression of CYP isoforms can produce wide differences in the metabolism of some compounds as compared with

individuals in the general population. This is in contrast to laboratory animals, where sex and strain can determine how an animal metabolizes a chemical.

Conclusions

Sex-dependent differences in xenobiotic metabolism are most pronounced in rats. Exaggerated sex-dependent variations in metabolism by rats may be the result of extensive inbreeding or differential evolution of CYP isoforms in mammals. Animal studies are used to help determine the metabolism and toxicity of many chemical agents in an attempt to anticipate the potential health risks of human exposure to these agents. One of the most important concepts to consider in using rodent studies to identify sensitive individuals in the human population is that human CYPs differ from rodent CYPs in both isoform composition and catalytic activities. Xenobiotic metabolism by male rats can reflect human metabolism when the compound of interest is metabolized by CYP1A or CYP2E because there is strong regulatory conservation of these isoforms between rodents and humans.

However, problems can arise when rats are used as animal models to predict the potential for sex-dependent differences in xenobiotic handling in humans. Information from countless studies has shown that the identification of sex-dependent differences in metabolism by rats does not translate across other animal species or humans. To date, sex-specific CYP isoforms have not been identified in humans. The lack of expression of sex-dependent CYP isoforms in humans indicates that the male rat is not an accurate model for the prediction of sex-dependent differences in humans. Differences in xenobiotic metabolism among humans are more likely the consequence of intraindividual variations as a result of genetics or environmental exposures rather than from sex-dependent differences in enzyme composition.

A major component of the safety assessment process is to identify, at the earliest stage possible, the potential for toxicity in humans. Earlier identification of individual differences in xenobiotic metabolism and the potential for toxicity will be facilitated by improving techniques to make better use of human tissues to prepare accurate in vitro systems such as isolated hepatocytes and liver slices to study xenobiotic metabolism and toxicity. Accurate systems should possess an array of bioactivation enzymes similar to the in vivo expression of human liver. In addition, compound concentrations and exposure times used in these in vitro test systems should mimic those achieved in the target tissues of humans. Consideration of such factors will allow the development of compounds with improved efficacy and low toxicity at a more efficient rate. The development of accurate in vitro systems utilizing human tissue will also aid in the investigation of the molecular mechanisms by which the CYP genes are regulated in humans. Such studies will facilitate our understanding of the basis for differences in the expression of CYP isoforms in humans.

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