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REVIEW

Temperature-dependent toxicity in mammals with implications for herbivores: a review

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Abstract Diet selection in mammalian herbivores is thought to be primarily governed by intrinsic properties of food, such as nutrient and plant secondary compound (PSC) contents, and less so by environmental factors. However, several independent lines of evidence suggest that the toxicity of PSCs is mediated, in part, by ambient temperature and that the effect of small changes in ambient temperature is on par with several fold changes in PSC concentration. This review describes the disparate lines of evidence for temperature-dependent toxicity and the putative mechanisms causing this phenomenon. A model is described that integrates thermal physiology with temperature-dependent toxicity to predict maximal dietary intake of plant secondary compounds by mammalian herbivores. The role of temperature-dependent toxicity is considered with respect to the observed changes in herbivorous species attributed to climate change. Possible future investigations and the effects of temperature-dependent toxicity on other endotherms are presented. Temperature-dependent toxicity has the potential to apply to all endotherms that consume toxins. The effects of temperature-dependent toxicity will likely be exacerbated with increasing ambient temperatures caused by climate change.

Keywords Mammalian herbivore · Temperature-dependent toxicity · Plant secondary compounds · Xenobiotics

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Abbreviations

CYP2B	Cytochrome p450 2B
LCT	Lower critical temperature
PSC	Plant secondary compound
TDT	Temperature-dependent toxicity
TNZ	Thermal neutral zone
UCT	Upper critical temperature

Introduction

The acquisition of food is a fundamental requirement for herbivores; reproduction, growth and maintenance are contingent on the fulfillment of this prerequisite. Intrinsic properties of food, such as nutrient and plant secondary compound (PSC) concentrations, play key roles in structuring the dietary strategies of herbivores (Dearing et al. 2005; Freeland and Janzen 1974; Marsh et al. 2006). Herbivores select food items from a variety of plant species and tissue types to satisfy nutrient requirements such as nitrogen and sodium (Robbins 1983). Although adequate intake of nutrients is critical to herbivore fitness, regulation of the ingestion of PSCs may hold even greater significance for diet selection in herbivores. Plants produce myriad secondary compounds, e.g., alkaloids, phenolics, terpenes, many of which are biologically active (Rosenthal and Berenbaum 1991). Ingestion of PSCs in excess of physiological limits can exact consequences that are far more immediate and deleterious than nutrient deficiencies (Dearing et al. 2005; Karasov and Martinez del Rio 2007). Knowledge of the critical intrinsic factors of plants is often powerful in predicting herbivore diet selection (Dearing 1996; Dearing and Schall 1992; Raubenheimer and Simpson 2009).

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Ambient temperature is an extrinsic factor not traditionally included in foraging theories of mammalian herbivores (Dearing 1996; Dearing and Schall 1992; Raubenheimer and Simpson 2009; Stephens and Krebs 1986). Because herbivorous mammals are endothermic, ambient temperature has not previously been considered to influence their feeding behavior to the same extent as their ectothermic herbivorous counterparts, whose foraging activity is a direct function of temperature (Bale et al. 2002). However, several independent lines of evidence suggest ambient temperature interacts with mammalian physiology to mediate the toxicity of PSCs and thereby alter diet selection. In general, increases in ambient temperature exacerbate the toxicity of xenobiotics like PSCs. The impact of ambient temperature on toxicity can be substantial. Small deviations in ambient temperature are on par with several fold changes in PSC concentration (Gordon 1993; Keplinger et al. 1959). Thus, environmental temperature gradients could sculpt diet selection in mammalian herbivores. Such temperature-dependent toxicity holds promise for partially explaining the recent changes in distribution, timing of reproduction and energy use of herbivorous mammals, particularly in arid regions of the world where warming is predicted to be greatest (IPCC 2007; Rowe et al. 2011; Moritz et al. 2008; Ozgul et al. 2010).

The intent of this review is to evaluate the potential effects of temperature-dependent toxicity on mammalian herbivores. First, various lines of evidence are reviewed on the role of ambient temperature on toxicity. Next, I present a hypothesis to explain the impacts of ambient temperature on toxicity with respect to thermoregulatory physiology of mammals. Putative mechanisms of temperature-dependent toxicity are then described. Finally, I explore the differential effects that temperature-dependent toxicity may have on a variety of mammalian herbivores as well as avian ones and outline questions for future research on this topic.

Evidence for temperature-dependent toxicity

The evidence for temperature-dependent toxicity stems from studies in the disciplines of pharmacology, agriculture and physiology. Across these disciplines, research in the area of temperature-dependent toxicity has largely been conducted in isolation from one another, yet taken together the results present a strong case for the generality of this phenomenon across mammals as a group. Mammalian herbivores are likely to be the group most subjected to this phenomenon since they regularly ingest foods containing toxins. However, this concept could apply to other mammals that consume toxic prey or are exposed to environmental contaminants.

Laboratory rodents and xenobiotics

The first line of evidence for temperature-dependent toxicity originated in pharmacological studies where laboratory rats (*Rattus norvegicus*) and mice (*Mus musculus*) were administered various xenobiotics via intraperitoneal injection. Researchers have repeatedly documented an effect of ambient temperature with respect to toxicity of various compounds including PSCs (Gordon 1993; Keplinger et al. 1959). The toxicity of pharmacological compounds in laboratory rodents is more often than not a function of ambient temperature with animals tolerating the highest doses at temperatures near 26 °C. At higher temperatures, less compound is needed to produce the desired effect. Temperatures lower than 26 °C also result in a reduction of the dose needed for toxicity, although not as frequently or to the same extent as higher temperatures (Gordon 1993; Keplinger et al. 1959). In a study of 58 xenobiotics, many of which were PSCs (e.g., caffeine, digitoxin, ephedrine), increases in ambient temperature increased the potency and toxicity of 55 compounds (Keplinger et al. 1959). For several different chemicals, a 10 °C difference in ambient from 26 to 36 °C produced an effect in rodents comparable to increasing the dose two- to eight-fold (Gordon 1993; Keplinger et al. 1959). For example, the lethal dose of caffeine (a PSC) in mice at 36 °C is one-fifth the lethal dose for mice at 26 or 8 °C (Table 1).

Laboratory mice often respond physiologically and behaviorally to toxic challenges (Gordon 1993; Gordon et al. 1988b). Mice at thermoneutrality or in the cold tend to reduce core temperature after being dosed with particular toxins. This phenomenon, known as regulated hypothermia, is thought to be an adaptive physiological response and not necessarily a pharmacological consequence of the xenobiotic (Gordon 1993). Furthermore,

Table 1 Fold change in the lethal dose for plant secondary compounds given to lab mice at different temperatures compared to the dose at 36 °C

Plant secondary compound	8 °C	26 °C
Acetyl salicylic acid	1.5	7.6
Atropine	5.1	7.6
Caffeine	5.1	5.1
Digitalis	1.5	2.1
Digitoxin	1.4	2.0
Ephedrine	3.5	1.5
Ethanol	2.3	1.5
Reserpine	2.3	5.1
Strychnine	1.0	6.0

Data from (Keplinger et al. 1959)

mice given toxic challenges prefer lower ambient temperatures when presented with a temperature gradient (Gordon 1993; Gordon et al. 1988a). The physiological reduction in core temperature coupled with the behavioral selection for lower ambient temperature enhances the probability of surviving a toxic insult (Gordon 1993).

These studies represent an extreme toxin challenge unlikely to be experienced by an animal in a more natural setting. That is, the endpoint of the experiment is often a lethal dose and the route of administration is intraperitoneal. Nonetheless, these studies demonstrate a pattern across many different xenobiotics, i.e., increases in ambient temperature can be on par with increases in dose. In general, xenobiotics are more toxic to mammals when administered at stressful ambient temperatures (just above thermoneutrality or close to freezing). While the dose and route of administration of the compounds are artificial, the temperatures used in these studies are well within those that animals experience under natural settings.

Domestic herbivores and fungal toxins

Domestic herbivores and ergot alkaloids provide another example of toxicity being a function of ambient temperature. Mammals ingest these alkaloids when they feed on tall fescue grass (*Lolium arundianceum*), infected with the fungal endophyte *Neotyphodium coenophialium*. Ingestion of these alkaloids by herbivores, particularly cattle, produces numerous negative physiological effects and the manifestation of symptoms is known collectively as "fescue toxicosis" (Aldrich et al. 1993; Cross et al. 1995). The effects of the ergot alkaloids are temperature dependent and are exacerbated at higher temperatures (30–35 °C) in laboratory rats and cattle (Aldrich et al. 1993; Osborn et al. 1992; Settivari et al. 2008a, b; Spiers et al. 2005). For example, in both rats and cattle, higher ambient temperatures reduces intake of a diet of ergot alkaloids to a greater extent than that observed at the same temperatures on control diets (Aldrich et al. 1993; Spiers et al. 2005). Since the toxic alkaloids are naturally produced and acquired in the diet, this system holds similarities to the PSCs confronted by mammalian herbivores.

A recent study explored the influence of temperature on the hepatic response of rats to ergot alkaloids (Settivari et al. 2009). They found differential expression of 200 genes in the liver, with the general pattern that rats at warmer temperatures exhibited reduced gene expression. Of the 14 differentially expressed genes pertaining to biotransformation of xenobiotics, 13 of these were down-regulated in animals under heat stress conditions. Down-regulated genes included many cytochromes P450 genes that are critical players in drug metabolism (Klaassen 2001; Settivari et al. 2008b). Moreover, rats subjected to ergot alkaloids at warmer temperatures exhibited lower rates of food conversion to body mass than those at cooler temperatures (Settivari et al. 2009; Spiers et al. 2005). The results are consistent with an impairment of the detoxification machinery under heat stress conditions. Overall, the results are consistent with the results of the pharmacological studies on mice and rats in that ergot alkaloids are more toxic at warmer temperatures.

Wild herbivores

The interplay of ambient temperature, PSCs and diet selection in natural plant–animal systems has been investigated in studies on *Neotoma albigula,* the white-throated woodrat. This species is a generalist herbivore, common in the Great Basin and Sonoran deserts (Macedo and Mares 1988). In areas of the Great Basin desert, juniper (*Juniperus monosperma*) composes 18–35 % of its diet (Dial 1988). Juniper is low in nitrogen and has notable levels of PSCs, particularly terpenes and phenolics (Adams et al. 1981; Nunez-Hernandez et al. 1989). Juniper intake by *N. albigula* is limited by PSC concentration and not low nutrient content (Dearing et al. 2000; Sorensen et al. 2005). In nature, the diet composition of *N. albigula* varies seasonally, with proportionally more juniper being consumed during the winter than the summer (Dial 1988). One hypothesis to explain the seasonal diet shift of *N. albigula* is that the reduced availability of herbaceous plants during the winter forces woodrats to rely more heavily on juniper. Alternatively, *N. albigula* may opt to ingest more juniper in the winter because of an interaction between ambient temperature, toxicity of PSCs and thermoregulation. The previous research supports this latter hypothesis. *Neotoma albigula* acclimated to 25 °C that were fed a juniper diet had relatively higher costs (50 %) of thermoregulation compared to woodrats acclimated to the same temperature but on a control diet lacking juniper (McLister et al. 2004). In contrast, *N. albigula* offered a juniper diet after acclimation to 18 °C, had lower relative thermoregulatory costs (24 %) than woodrats at the same temperature eating a control diet lacking juniper. From a thermoregulatory perspective, the ingestion of juniper by *N. albigula* appears to be beneficial at cooler temperatures but detrimental at warmer temperatures. These results suggest that *N. albigula* should modulate juniper intake with respect to ambient temperature. In fact, when this species was allowed to select its diet from *ad lib* quantities of a juniper diet and a non-toxic diet offered simultaneously, it consumed proportionally and absolutely more juniper diet at the cooler temperature than at warmer temperature (Dearing et al. 2008; Fig. 1). Thus, the quantity of juniper ingested by woodrats appears to be more a function of ambient temperature than the availability other non-toxic food.

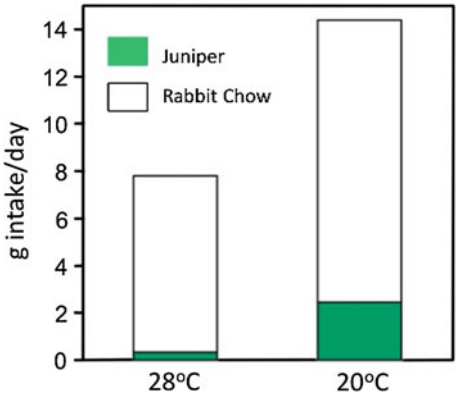

Fig. 1 Intake of juniper (*green*) and rabbit chow (*white*) by *N. albigula* acclimated to different ambient temperatures. Data from Dearing et al. (2008) (color figure online)

Putative mechanisms

The underlying mechanisms through which elevated temperatures intensify the effects of toxins in mammals are currently speculative. Liver size (relative and absolute) tends to decrease with acclimation to warm temperatures (Settivari et al. 2008a; Toloza et al. 1991). The reduction in organ size at warmer temperatures could reduce an animal's total capacity to metabolize toxins. However, changes in liver size cannot fully account for this phenomenon because temperature-dependent toxicity is observed in animals not acclimated to the experimental temperature. That is, compounds are more toxic at warmer temperatures compared to cooler ones in animals with similar liver sizes (Keplinger et al. 1959). Moreover, the greatest tolerance to compounds was not observed at the lowest temperature (8 °C), where liver organ mass should be greatest, but at a temperature (26 °C) a few degrees below the thermal neutral zone (TNZ, Table 1, Gordon 1993).

Temperature-dependent changes in toxicity seem to be primarily mediated by a reduction in overall liver metabolism at temperatures above the thermal neutral zone (Kaplanski and Ben-Zvi 1980; Ben-Zvi and Kaplanski 1980; Settivari et al. 2009). The enzyme activities of key biotransformation enzymes are reduced in the livers of rodents acclimated to warm temperatures compared to cooler ones (Kaplanski and Ben-Zvi 1980; Pachecka et al. 1983). A recent study explored the influence of temperature on the hepatic response of rats to ergot alkaloids using transcriptomics, and found reduced gene expression of ~150 genes in rats exposed to temperatures above the TNZ (heat stress) compared to those within the TNZ (Settivari et al. 2009). Of the 14 differentially expressed detoxification genes pertaining to biotransformation of xenobiotics, 13 of these were down-regulated in animals under heat stress conditions. The results are consistent with an impairment of the detoxification machinery under heat stress conditions. The liver is one of the most sensitive organs to heat stress and an increase in oxidative damage may be the cause of the reduced liver function at higher environmental temperatures (Flanagan et al. 1995; Zhang et al. 2003). Indeed there appears to be cross-talk from the liver to the brain such that when the liver reaches a critical temperature, food intake ceases (De Vries et al. 1993). Furthermore, the diversion of blood flow to the periphery to promote cooling during heat stress may reduce blood flow to the viscera, further reducing metabolism of the liver (Hales et al. 1979).

At ambient temperatures lower than the TNZ, the heat generated during the liver's basic functions of nutrient and toxin processing may simultaneously serve to maintain core temperature. An example of this is observed in *N. albigula,* an herbivorous woodrat. Animals acclimated to 18 °C had lower relative thermoregulatory costs as rate when ingesting PSCs compared to a control diet lacking PSCs (McLister et al. 2004). In contrast, woodrats acclimated to 25 °C had much greater thermoregulatory costs when ingesting dietary PSCs compared to a control diet. While this difference in metabolic costs may have been a direct consequence of the PSCs acting on the circulatory system or the gut microbiota (McLister et al. 2004), it is also possible that the metabolism of PSCs in the liver generated heat more efficiently than in the absence of PSCs.

Integrating temperature-dependent toxicity and thermophysiology

Temperature-dependent toxicity may be a predictable function of an animal's thermal state. The metabolic rate of an endotherm varies with ambient temperature where metabolic rates are highest at temperature extremes and lowest at intermediate temperatures (Fig. 2; Schimdt-Nielsen 1997). For many species, there is often a several degree range of intermediate ambient temperatures across which metabolic rate remains reasonably constant as well as low. This range of ambient temperatures is referred to as the animal's TNZ and is punctuated by a lower critical temperature (LCT) and an upper critical temperature (UCT). The extent of the TNZ is dependent on a number of factors including body size, fur thickness and body shape (Schimdt-Nielsen 1997). The processing of toxins is not a simple positive function of metabolic rate because at high metabolic rates, such as those above the UCT, the effective dose decreases dramatically. In contrast, the even higher metabolic rates observed when animals are held at temperatures several degrees below the LCT do not always result in an increase in the dose to effect (Table 1). The

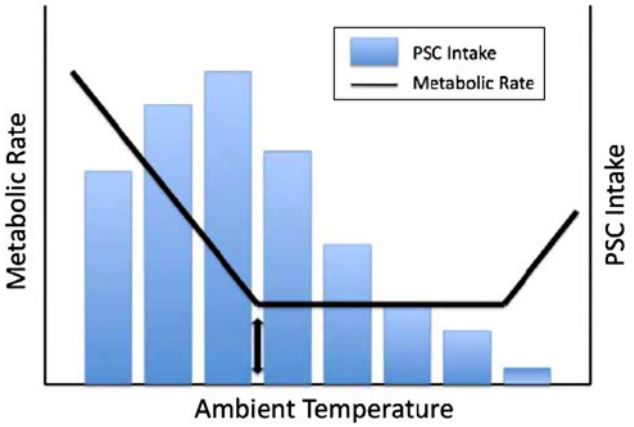

Fig. 2 The hypothetical relationship between ambient temperature and PSC ingestion. Herbivores are predicted have the greatest intake of PSCs at ambient temperatures below the lower critical temperature (indicated by the *arrow*)

pattern that emerges from the data suggests that an animal's ability to process toxins appears to be greatest at ambient temperatures just below its TNZ and lowest at temperatures above its TNZ, or warmer temperatures (Fig. 2; Gordon 1993; Kaplanski and Ben-Zvi 1980; Keplinger et al. 1959; Settivari et al. 2008b).

Based on these data, I propose that ambient temperature mediates tolerance to PSCs in herbivores such that PSC intake is a function of the interplay between environmental temperature and the animal's thermal state (Fig. 2). I predict that herbivores will ingest the highest doses of PSCs at temperatures slightly lower than their lower LCT and the lowest doses at ambient temperatures above the TNZ (Fig. 2). PSC intake is predicted to decline at temperatures well below the LCT but not to the extent observed at temperatures above the UCT. These predictions are based on a synthesis of the patterns observed across disparate studies. First, in studies on ingestion of juniper by woodrats at different temperatures, the cool thermal treatments where juniper ingestion was greatest, were 5–7 °C below thermoneutrality (Dearing et al. 2008). In contrast the warm thermal treatments (25, 28 °C) were either at the LCT or within the TNZ, respectively. The studies on temperature-dependent toxicity in laboratory rodents document a similar pattern of toxicity and temperature with respect to the TNZ (Gordon 1993; Kaplanski and Ben-Zvi 1980; Keplinger et al. 1959; Settivari et al. 2008b). The mechanism underlying the differential tolerance to PSCs across temperatures is predicted to be the same as that proposed for differences in toxicity of pharmacological compounds. That is, at temperatures above the TNZ, liver function is impaired. The parallel results of these studies beg investigation into the generality of this response in mammalian herbivores.

Future investigations

The evidence suggests that temperature-dependent toxicity should apply to all endotherms that consume toxins. However, the data on this phenomenon are limited to a few species of laboratory rodents, domestic mammals and one wild herbivorous rodent (Cross et al. 1995; Dearing et al. 2008; Gordon 1993; McLister et al. 2004; Settivari et al. 2008a). Future investigation into temperature-dependent toxicity could explore this trend in a number of taxa. Hundreds of mammalian species are herbivorous, many of which for the most part cannot completely avoid ingestion of dietary toxins. Herbivory is less common among birds; however, the ingestion of PSCs has been documented for several herbivorous birds. Grouse species and the hoatzin are examples of bird species that consume notable quantities of PSCs (Dominguez-Bello et al. 1994; Jakubas et al. 1989). Birds and mammals that feed on toxic prey, such as scorpions and snakes, may also be affected (Feldhamer et al. 2007; Welty and Baptista 1988). Numerous large bodied insects are herbivorous and endothermic (Heinrich 1993). Determining the extent of temperature-dependent toxicity will require further study across these taxonomic groups.

Mammalian herbivores often consume different diets over the course of the year (Bryant and Kuropat 1980; Crawford 1982; Dearing 1996; Jakubas et al. 1989; Kawamichi 1997; Nixon et al. 1968; Westoby 1980). Pikas, rabbits, grouse, deer, and squirrels are just a few examples of animals that have been documented to have diets that change with season. Plant availability is often given as the cause for such dietary shifts. While this factor may play a leading role, the temperature differences across seasons may also influence diet selection through temperature-dependent toxicity. Herbivores may be able to ingest greater levels of PSCs during the winter months and ingestion of these compounds may provide a thermoregulatory benefit. Thus, diet selection may change seasonally independent of food availability. Future studies could evaluate the relative contributions of temperature-dependent toxicity and food availability with respect to diet selection.

Climate change and temperature-dependent toxicity

Climate change is having notable effects on endotherms. Changes in distribution, community structure, timing of reproduction and energy use are just a few examples of the documented impacts (Ozgul et al. 2010; Rowe et al. 2011; Sheldon et al. 2011). Herbivorous species appear to be particularly vulnerable to changes in temperature (Moritz et al. 2008; Ozgul et al. 2010; Rowe et al. 2011; Sheldon et al. 2011). While the effects of climate change are likely

caused by a suite of factors, temperature-dependent toxicity could contribute in part to the observed changes. The adequate intake of energy and nutrients is a fundamental requirement of all animals, with insufficient quantities of food having serious consequences for organisms (Karasov and Martinez del Rio 2007). Temperature-dependent toxicity has the potential to reduce an animal's ability to acquire sufficient amounts of food if the food contains toxins and ambient temperature is within or above the animal's TNZ. Given that most herbivores consume PSCs in their diet, the increases in ambient temperature caused by climate change could impact a large number of herbivorous species. Understanding the interplay of temperature and diet will be imperative to predict the response of mammalian herbivores to climate change.

Mammals living in seasonal environments experience a range of temperatures above and below their TNZ over the course of a year. If temperature-dependent toxicity is a fundamental property of mammalian herbivores, then summer temperatures should impose the greatest constraint on ingestion of PSCs because these temperatures will likely fall within or above the TNZ. Ambient temperature increases mediated by climate change may extend the length of time during which herbivores must avoid or reduce ingestion of toxins.

Whole organism approaches

While demonstrating an effect of ambient temperature on liver function is critical in understanding the mechanism underlying temperature-dependent toxicity, scaling this organ level effect to the whole organism is also important. Food intake and diet selection should be impacted by ambient temperature. Given that most mammalian herbivores are mobile enough to find microhabitats of different temperatures, it will be interesting to determine if animals can circumvent average temperatures that may be prohibitive to ingestion dietary toxins by ingesting foods in cooler microhabitats or by shifting their feeding patterns to cooler periods of the day. The use of small temperature recording devices (e.g., "iButtons" by Embedded Data Systems) may be useful in documenting an animal's environmental profile while foraging. It will also be important to understand the role of long-term temperature acclimation and whether acclimation can mitigate effects of temperature-dependent toxicity. Lastly, many endotherms are capable of transient heterothermy (Feldhamer et al. 2007; Schimdt-Nielsen 1997), where body temperature oscillates considerably during the course of a day. Such changes in body temperature are similar to the regulated hypothermic response observed in laboratory rodents given toxins. Regulated hypothermia is thought to be an adaptive response that reduces the effect of ambient temperature (Gordon 1993). Thus, animals capable of short-term heterothermy may be able to circumvent temperature-dependent toxicity by lowering body temperature after ingesting toxins. More research in this area is warranted to understand the effects of temperature-dependent toxicity in endotherms.

Use of hypnotic state assays

Documenting the impact of temperature on detoxification is conventionally approached through estimates of liver activity, such as enzyme activity assays or gene expression techniques. While these techniques provide detailed information for particular enzymes, they typically require euthanizing the subject to remove the liver for testing, which may not be an option for all species. However, a non-destructive method exists for measuring overall liver activity. Administration of a hypnotic agent resulting in anesthesia and measurement of the length of time the animal remains anesthetized is an indicator of general liver metabolism (Kim and Shin 2005; Sasaki 1994). These assays have been used to compare detoxification rates of herbivores as well as to screen for possible interactions between drugs in nutraceutical or pharmacological studies (Dearing et al. 2006; Desjardins and Iversen 1995; Price et al. 2004; Kim and Shin 2005; Sasaki 1994; Atal et al. 1985). The hepatic enzymes that metabolize the commonly used hypnotic agents are the same enzymes that metabolize PSCs. For example, cytochromes P450 in the subfamily 2B (CYP2B) metabolize hexobarbital, a commonly used hypnotic agent (Jori et al. 1970; Lewis and Lake 1997; Waxman and Azaroff 1992). The CYP2B subfamily in mammalian herbivores is known to play a crucial role in the metabolism of PSCs across many plant species (Haley et al. 2007a, b; El-Merhibi et al. 2007; Magnanou et al. 2009; Skopec et al. 2007).

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