

How Do Predators Cope With Chemically Defended Foods?

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Abstract. Many prey species (including plants) deter predators with defensive chemicals. These defensive chemicals act by rendering the prey's tissues noxious, toxic, or both. Here, I explore how predators cope with the presence of these chemicals in their diet. First, I describe the chemosensory mechanisms by which predators (including herbivores) detect defensive chemicals. Second, I review the mechanisms by which predators either avoid or tolerate defensive chemicals in prey. Third, I examine how effectively free-ranging predators can overcome the chemical defenses of prey. The available evidence indicates that predators have mixed success overcoming these defenses. This conclusion is based on reports of free-ranging predators rejecting unpalatable but harmless prey, or voluntarily ingesting toxic prey.

Introduction

Many plants and animals lace their tissues with noxious chemicals (Harborne, 1988; Whitman *et al.*, 1990), which are not only diverse in chemical structure (Blum, 1981; Harborne and Baxter, 1993), but also in mode of action. Some irritate or burn mucous membranes, some generate aversive tastes or odors, some produce toxic effects, and many elicit a combination of these effects (Eisner, 1970; Freeland and Janzen, 1974; Fowler, 1983; Whitman *et al.*, 1990; Glendinning, 1994). This article explores how mammalian carnivores, insectivores, and herbivores (henceforth, predators) cope with the presence of these defensive chemicals in their diet. For the sake of simplicity, I refer to the different types of predator foods (*i.e.*, plant and animal tissues) as prey. I focus on four issues: (a) the challenges

that defensive chemicals pose to predators; (b) the chemosensory and tactile mechanisms for detecting defensive chemicals; (c) the behavioral and physiological mechanisms for tolerating defensive chemicals in prey; and (d) the extent to which predators are able to breach chemical defense systems without suffering dire consequences.

The Predator's Dilemma

It is difficult for modern humans to appreciate the challenges that chemically defended foods pose to free-ranging predators. This is because the human diet consists of a highly selective collection of foods, many of which have been subjected to decades of artificial selection for high palatability and low toxicity (Johns, 1990). Any residual noxious compounds in foods are further reduced through a variety of processing techniques, including washing, cooking, enzymatic treatment, or solvent extraction (Johns, 1990). The situation for free-ranging predators is entirely different. Nearly 10% of all terrestrial plant species contain toxic alkaloids, and an even greater percentage contains toxic glycosides (Kingsbury, 1964). Further, more than half of all insect orders contain species with chemical defenses (Whitman *et al.*, 1990). One study examined the entire plant fauna at four sites on the Caribbean island of Aruba for the presence of poisons (*i.e.*, phenolics, saponins, alkaloids, and cyanogenic compounds) (Schall and Ressel, 1991). Among the plant species that were of a size and texture to be eaten by the local herbivore (an endemic whiptail lizard, *Cnemidophorus arubensis*), 63% contained poisons, and the lizards avoided most of these toxic ones. These observations illustrate that chemically defended prey can constitute a substantial proportion of the available foods in a habitat.

The abundance of chemically defended prey often forces predators to choose between two unsatisfactory alternatives:

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starve or eat a potentially toxic prey item. There is no easy solution to this dilemma. Predators must cope with active and passive defense strategies. For the active strategy, prey respond to potential predators by spraying caustic chemicals, releasing incapacitating or toxic vapors, secreting toxic fluids over their bodies, or injecting venom with a stinger (Eisner, 1970; Whitman *et al.*, 1990; Goddard, 2000). The act of injecting venom not only can produce tissue necrosis, but it can also elicit an allergic reaction, initiate an infectious disease process, or lead to a secondary infection (Goddard, 2000). For the passive strategy, prey store noxious chemicals in their tissues, which predators encounter during the initial stages of their attack (Freeland and Janzen, 1974; Blum, 1981; Rosenthal and Berenbaum, 1992). In many cases, these chemicals deter predators by generating aversive chemosensory or toxic effects; in some cases, they kill the predators outright (Freeland and Janzen, 1974; Whitman *et al.*, 1990; Glendinning, 1994; Knight *et al.*, 1999).

Predators use a variety of mechanisms to cope with defensive chemicals. These include chemosensory mechanisms (in the oral cavity, intestinal tract, and central nervous system) that elicit aversive responses when stimulated; learning mechanisms that work in collaboration with the chemosensory mechanisms to identify prey that are safe to eat; and physiological and behavioral mechanisms that increase tolerance to particular poisons. Below, I review our current understanding of how these different mechanisms function.

Chemosensory Mechanisms for Detecting Defensive Chemicals

All animals appear to possess chemosensory mechanisms for detecting and rejecting potentially toxic compounds. This inference is based on the fact that all animal taxa studied to date exhibit an immediate aversive response to foods treated with quinine and/or strychnine. The taxa that have been studied include mammals (Garcia and Hankins, 1975; Glendinning, 1994), birds (Rensch and Neunzig, 1925), fish (Bardach and Case, 1965), reptiles (Cooper *et al.*, 2002), amphibians (Bowerman and Kinnamon, 1994), insects (Dethier, 1976), molluscs (Wells, 1963), annelids (Laverack, 1960; Li *et al.*, 2001), tunicates (Hecht, 1918), and echinoderms (Olmsted, 1917). Here, I will focus on mammals, as their chemosensory mechanisms have been characterized most extensively.

Orosensory mechanisms

Taste. The taste system serves as the final arbiter of whether a substance should be swallowed. This sensory system is served by three nerves, each of which contains neurons that contact individual taste cells within taste buds (Finger and Simon, 2000). Two branches of the facial (7th cranial) nerve, the chorda tympani and greater superficial petrosal,

together innervate taste buds in the anterior portion of the tongue, nasoincisor ducts, soft palate, and—in the rat—the Geschmacksstreifen (a taste strip at the junction of the hard and soft palate). A branch of the glossopharyngeal (9th cranial) nerve innervates taste buds in the posterior tongue and soft palate. Finally, the vagus (10th cranial) nerve innervates taste buds in the pharynx, epiglottis, and upper esophagus. Each taste cell exhibits varying degrees of responsiveness to specific classes of taste stimuli (*e.g.*, bitter, sour, sweet, salty, or umami (Sato and Beidler, 1997; Caicedo and Roper, 2001; Gilbertson *et al.*, 2001; Caicedo *et al.*, 2002).

Because many naturally occurring poisons taste bitter to humans (and elicit aversive responses in other mammals), the bitter taste system is thought to constitute an important mechanism for identifying poisonous foods (Bate-Smith, 1972; Garcia and Hankins, 1975). A family of about 30 taste receptors, called the T2Rs (Bachmanov and Beauchamp, 2007), was discovered recently in mice and humans (Chandrashekar *et al.*, 2000; Bufe *et al.*, 2002). These T2Rs bind selectively to bitter taste stimuli, and each T2R appears to have a relatively narrow and distinct molecular receptive range (for review, see Meyerhof, 2005). Further, selective stimulation of the taste cells expressing T2Rs is sufficient to elicit a strong aversive response in mice (Mueller *et al.*, 2005).

Given that many foods taste bitter but are harmless (Bate-Smith, 1972; Brower, 1984; Brieskorn, 1990; Glendinning, 1994), predators (particularly herbivorous ones) would drastically limit their range of potential food items by rejecting everything that tastes bitter (Glendinning, 1994). For this reason, animals would benefit from an ability to differentiate among bitter foods. Several investigators have examined bitter taste discrimination, but their findings are contradictory. Some studies indicate (a) that all bitter taste stimuli should generate indiscriminable afferent signals because each bitter-sensitive taste cell expresses multiple classes of T2R (Chandrashekar *et al.*, 2000); and (b) that animals cannot discriminate between isoaversive concentrations of different bitter taste stimuli (Aspen *et al.*, 1999; Spector and Kopka, 2002). Other studies indicate (a) that individual bitter-sensitive taste cells do discriminate among bitter taste stimuli (Caicedo and Roper, 2001); (b) that different bitter taste stimuli generate distinct across-fiber patterns in the primary afferent neurons (Dahl *et al.*, 1997); and (c) that gustatory adaptation to one bitter taste stimulus does not always cross-adapt to other bitter taste stimuli (McBurney *et al.*, 1972). Irrespective of how these contradictory findings are resolved, the capacity to discriminate bitter taste stimuli is not necessary for distinguishing toxic and nontoxic foods in nature. This is because two bitter-tasting foods that differ in toxicity would probably also differ in many other flavor attributes (*e.g.*, taste, odor, and mouth-feel). An animal could learn to avoid the toxic food

by conditioning an aversion to its unique flavor attributes (Touzani and Sclafani, 2002).

Somatosensation. The somatosensory system in the oral cavity, nose, and eyes is served primarily by branches of the trigeminal (5th cranial) nerve. These branches contain axons of varying sizes. The A- β (myelinated) fibers terminate in specialized end-organs (*i.e.*, Merkel disks, Meissners corpuscles, Krause end-organs, and paciniform endings) or as free nerve endings. They respond primarily to mechanical stimulation (Bryant and Silver, 2000; Finger and Simon, 2000). A- β fibers are particularly abundant in the mouth and provide information about both the physical attributes of foods (*e.g.*, texture, consistency, and location) and the condition of the oral mucosa (*e.g.*, its lubricity). Two other classes of trigeminal fibers (myelinated A- δ and non-myelinated C fibers) terminate as free nerve endings in the mouth, nose, and eyes. Most of these fibers are polymodal—that is, they respond to thermal, mechanical pain, and chemical stimulation (Bryant and Silver, 2000; Finger and Simon, 2000). A final class of trigeminal fibers forms synaptic contacts with solitary chemoreceptor cells in the nasal cavity of mice (and perhaps other predators) (Zancanaro *et al.*, 1999; Finger *et al.*, 2003). These chemoreceptor cells express T2R channels and respond to compounds that humans describe as noxious (*e.g.*, denatonium, quinine, and cycloheximide) (Finger *et al.*, 2003). Stimulation of these chemoreceptor cells inhibits inhalation.

The term chemesthesis is used to encompass the somatosensory sensations elicited by chemical stimuli (Green *et al.*, 1990). The chemesthetic sensations in the mouth and nose vary considerably with chemical type and concentration; they include heat, cold, pain, irritation, itching, bitter, stinging, tingling, and numbness (Jacobson, 1948; Rozin and Schiller, 1980; Greger, 1984; Bryant and Mezine, 1999; Tanua *et al.*, 2001; Green and Schullery, 2003; Sugai *et al.*, 2005; Lim and Green, 2007). These sensations are thought to be mediated in large part by chemically induced modulation of ion flow through TRP, ASIC, and Na⁺ channels in the distal dendritic tips of myelinated A- δ and non-myelinated C fibers (Bryant and Silver, 2000; Caterina and Julius, 2001; Jordt *et al.*, 2004; Bautista *et al.*, 2005).

Some ingested chemicals (*e.g.*, tannins) create a sensation of dryness or roughness in the mouth, which humans refer to as “astringency” (Bate-Smith, 1954). Tannins, one of the most abundant classes of defensive compound in plants (Swain, 1979; Bernays *et al.*, 1989), generate this sensation by precipitating or cross-linking the mucoproteins in saliva; this reduces lubricity and thereby increases friction between mouthparts (*e.g.*, tongue and palate) (Green, 1983; Breslin *et al.*, 1993; Prinz and Lucas, 2000). Humans consider astringency to be pleasant at low intensities (*e.g.*, in red wines), but aversive at high intensities (Joslyn and Goldstein, 1964; Arnold *et al.*, 1980). Tannins are aversive to

many species of predators, across a wide range of concentrations (Mole and Waterman, 1987; Fleck and Layne, 1990; Glendinning, 1992b). Because astringency stems from a physical effect of the tannins on saliva, it is likely that this sensation occurs in non-human mammals as well. This inference is supported by the observation that the aversiveness of tannins to mice is reduced by the induction of high levels of salivary proline-rich proteins (PRPs) (Glendinning, 1992b). The PRPs are thought to bind to tannins in the oral cavity, thereby diminishing their astringent effects (Hagerman and Butler, 1981; Mehansho *et al.*, 1985; Austin *et al.*, 1989).

Most species of mammal exhibit strong and sustained aversions to foods that elicit strong chemesthetic or astringent sensations (Mason *et al.*, 1991; Wagner and Nolte, 2000; Epple *et al.*, 2001, 2004; Tewksbury and Nabhan, 2001). In some cases, predators would benefit by avoiding these foods. For instance, insects produce a prodigious array of defensive exudates, which are intensely odoriferous (*e.g.*, E-2-hexenal, salicylaldehyde), highly reactive (*e.g.*, benzoquinone), cytotoxic (*e.g.*, formic acid), lesion-forming (cantharidin, pederin), or hot and caustic (oxidized hydroquinones) (Eisner, 1970, 1980; Blum, 1981; Whitman *et al.*, 1986; Whelan and Weir, 1987). A single encounter with many of these defensive exudates can condition long-lasting aversions or even kill the predator outright (Eisner, 1970; Whitman *et al.*, 1990). Further, at high concentrations, tannin-rich foods can produce systemic toxicity (Mueller-Harvey, 2006). It is notable, however, that many of the spices (*e.g.*, chili pepper, black pepper, horseradish, and ginger) and brewed beverages (*e.g.*, coffee and tea) that humans consume regularly are strong stimulants of the oral somatosensory system. The fact that these spices and beverages are relatively harmless shows that intense stimulation of the oral somatosensory system does not reliably signal toxicity.

Olfaction. When an animal sniffs or masticates food, odors are carried *via* air currents to the olfactory epithelium in the dorsal region of each nasal cavity. Then, the odors must traverse a watery boundary layer on the nasal epithelium before contacting G-protein-coupled receptors on the cilia of olfactory neurons. Neural signals generated in the cilia of olfactory neurons are relayed to the olfactory bulb *via* axonal process that project through the cribriform plate of the skull and synapse in glomeruli within the olfactory bulb (Christensen and White, 2000). Molecular studies in mice have revealed (a) that each olfactory neuron expresses a single olfactory receptor; (b) that all of the olfactory neurons that express the same olfactory receptor project to the same glomerulus; and (c) that each class of olfactory receptor type binds multiple odors (Mombaerts, 2001; Breer, 2003). Accordingly, each glomerulus receives convergent input from thousands of olfactory neurons express-

ing the same olfactory receptor type. This organizational plan should provide higher cortical centers in the mouse with a combinatorial code by which to identify and discriminate thousands of odors (Buck, 1996).

The olfactory and nasal trigeminal systems are anatomically distinct. Nevertheless, they are functionally inter-related because most chemicals that stimulate one system also stimulate the other (Cometto-Muñiz and Cain, 1998; Cometto-Muñiz *et al.*, 1998; Dalton, 2003). This overlap should not be taken to indicate that the two systems are redundant, however. The olfactory system responds to low concentrations of most volatile compounds (Cometto-Muñiz *et al.*, 1998; Dalton, 2001) and thus may serve as a type of sentinel (or early warning system) for chemically defended prey, keeping the predator at a safe distance. In the event that this early warning system fails and the predator approaches a noxious prey, then the nasal trigeminal system would serve as a secondary warning system. Given that some insect defensive secretions are so toxic that their vapors alone can incapacitate a predator (Whitman *et al.*, 1990), this two-tiered warning system may be highly beneficial in some contexts. However, in the absence of a clear relationship between stimulus quality (*e.g.*, degree of pleasantness) and toxicity, predators may be incapable of discriminating harmless and harmful volatile defensive compounds based on odor and trigeminal input alone. Predators may thus need to assess toxicity through trial and error.

The olfactory system could help predators avoid toxic foods in other ways. For example, many toxic plants and insects emit distinctive odor cues (*e.g.*, pyrazines), which generate unusually persistent memories (Woolfson and Rothschild, 1990; Rothschild *et al.*, 1994). Accordingly, any predator that attacks a chemically defended prey and survives could form a long-lasting association between its salient odor (*e.g.*, the odor of pyrazines) and its aversive chemosensory/toxic effects, causing it to avoid prey with similar odor signatures in the future (Camazine, 1985).

Post-oral chemosensory mechanisms

Gastrointestinal tract. Oral and nasal chemosensory mechanisms for avoiding toxic foods are not foolproof. For instance, the aversive taste of many bitter compounds can be masked (partially or completely) by the presence of carbohydrates (Kappauf *et al.*, 1963; Lawless, 1979; Stevens, 1996) or sodium (Breslin and Beauchamp, 1995, 1997). Further, after adapting to the taste of one harmless bitter taste stimulus (Warren and Pfaffman, 1959; London *et al.*, 1979; Zellner *et al.*, 1985; Harder *et al.*, 1989), animals are often less sensitive to the taste of other bitter (and potentially toxic) compounds (McBurney *et al.*, 1972; Moskowitz *et al.*, 1975; Keast and Breslin, 2002). In these scenarios, predators would benefit from a back-up “bitter taste” system in their gastrointestinal tract.

There are four lines of support for an extensive, but diffuse, network of chemosensory cells in the gastrointestinal tract of mice and rats, which sense bitter (and thus, potentially toxic) substances. First, some of the chemosensory cells in the gut express the same signaling proteins that mediate bitter taste in the oral cavity. These signaling proteins include the T2Rs (Höfer *et al.*, 1996; Höfer and Drenckhahn, 1998; Wu *et al.*, 2002; Rozengurt, 2006) and several downstream transduction proteins (α -gustducin, PLC β 2, and Trpm5; Höfer *et al.*, 1996; Höfer and Drenckhahn, 1998; Dyer *et al.*, 2005; Bezençon *et al.*, 2007; Kaske *et al.*, 2007; Sutherland *et al.*, 2007). Second, two T2R ligands (phenylthiocarbamide and denatonium benzoate) induce Ca^{2+} signaling and CCK release in enteroendocrine STC-1 cells (Chen *et al.*, 2006). Third, gastric infusion of one bitter taste stimulus (denatonium) elicits a strong excitatory response in the rat’s abdominal vagus nerve (Uneyama *et al.*, 2004), which relays afferent input from chemosensory cells in the gut to the brainstem (Schwartz and Moran, 1998). Fourth, bitter stimuli elicit a concentration-dependent decrease in stomach contractions when infused intragastrically in dogs (Carlson *et al.*, 1914–15; Moorhead, 1915).

My colleagues and I recently asked (a) whether rats and mice would condition an aversion to a sweetened fruit flavor when its consumption was paired with intragastric infusions of a relatively harmless bitter taste stimulus (denatonium); and (b) whether intragastric infusions of denatonium would delay gastric emptying (Glendinning *et al.*, 2007). We found that the intragastric denatonium infusions not only conditioned strong flavor aversions in rats and mice, but they also delayed gastric emptying. This study provides the first evidence that rodents respond to the presence of “bitter” substances in their gastrointestinal tract by generating both behavioral and physiological responses

Area postrema. The area postrema (AP) is a brainstem nucleus located near the obex at the caudal tip of the fourth ventricle (Miller and Leslie, 1994). Stimulation of the AP elicits vomiting. This stimulation can arise from vagal afferents originating in the gastrointestinal wall (Saito *et al.*, 2003) or from a chemoreceptor trigger zone within the AP (Gaitondé *et al.*, 1965; Miller and Leslie, 1994). Because the AP lacks a blood-brain barrier, its chemoreceptor trigger zone can sense compounds dissolved in the blood and cerebral spinal fluid. Little is known about the nature of the AP chemoreceptors, but they are known to respond to a diverse range of naturally occurring poisons (or drugs) in the blood, including cardiac glycosides, apomorphine, morphine, and lobeline (Gaitondé *et al.*, 1965; Miller and Leslie, 1994; Andrews and Horn, 2006). In some species, the AP responds to the presence of poisons by eliciting vomiting. This observation led Davis *et al.* (1986) to hypothesize

that the AP constituted a third line of defense against defensive chemicals in foods.

There are significant gaps in our understanding of how the AP functions in free-ranging animals. For instance, little is known about the molecular receptive range or sensitivity of the AP to defensive chemicals. To what extent does the molecular receptive range of the AP overlap with that of the chemosensory systems in the mouth and gut? Are the chemosensory systems in the mouth and gut more or less sensitive than those in the AP to ingested poisons? Why can some species of mammal vomit (*e.g.*, cat, dog, ferret, humans, cattle, primates, and shrews) and others cannot (*e.g.*, mouse, rat, hamster, and many ruminants) (Andrews and Horn, 2006)?

Mechanisms for Avoiding Defensive Chemicals in Prey

Predators exhibit a variety of behavioral and physiological mechanisms for avoiding toxic foods. Many of these avoidance measures incorporate the chemosensory mechanisms discussed above. While some of these measures involve individual learning, others require the presence of conspecifics.

Individual learning about what to avoid

Garcia and Hankins (1975) proposed two “cardinal rules” that predators should follow to avoid poisoning themselves. The first rule is to avoid anything that tastes unpalatable, particularly if it is bitter. This rule is supported by the observations that virtually all naturally occurring poisons taste bitter to humans (Bate-Smith, 1972; Garcia and Hankins, 1975; Brower, 1984; Brieskorn, 1990), and most chemicals that taste bitter to humans also elicit an aversive response in other mammals (Glendinning, 1994). The second cardinal rule is to consume novel foods cautiously (particularly bitter ones), limiting intake to a few bites; and to feed avidly on new foods only after repeated nibbling has failed to produce postingestive malaise. This second rule is supported by the observations that (a) many wild and domestic rats sample novel foods cautiously, and as a result, are difficult to poison (Chitty and Shorten, 1946; Rzóska, 1953; Barnett, 1956); and (b) when a food (particularly a novel one) generates postingestive malaise, predators often condition an aversion to it (Garcia *et al.*, 1985; Zahorik *et al.*, 1990; Provenza *et al.*, 1992).

Another mechanism for avoiding defensive compounds is to feed selectively on the most palatable tissues. This strategy should be effective when the defensive compounds can be detected by oral or nasal chemosensory systems, and when the concentration of defensive compounds varies across individuals within a prey species or across body parts within an individual prey. In support of this prediction, predators have been reported to feed selectively on individual prey with the lowest concentration of defensive chem-

icals (Oates *et al.*, 1977; Glander, 1981; Cooper and Owen-Smith, 1985; Meyer and Karasov, 1989; Pass *et al.*, 1998; Moore and Foley, 2005) and on the most poorly defended body parts of individual prey (Benson and Borell, 1931; Kenagy, 1972; Glander, 1981; Reichardt *et al.*, 1984; Tahvanainen *et al.*, 1985; Clausen *et al.*, 1986; Glendinning, 1990).

Learning from others about what to eat

A young mammal can learn which foods are safe from its mother and other conspecifics (Galef and Beck, 1990). Mothers transmit their food habits by means of food flavors in the womb, milk, and fecal pellets (Galef and Clark, 1972; Galef and Sherry, 1973; Bilkó *et al.*, 1994; Semke *et al.*, 1995), and during communal foraging sessions during the weaning process (Provenza *et al.*, 1992; Valsecchi *et al.*, 1992). Once a young mammal separates from its mother, it can also observe conspecifics (or “demonstrators”). For example, Norway rats develop preferences for a food after interacting with a demonstrator rat that has recently eaten that food; this socially transmitted diet preference is enhanced by carbon disulfide carried on the breath of the demonstrator rat (Galef *et al.*, 1988). Living in a stable social group also appears to help young individuals locate safe foods. This is illustrated by the observation that frugivorous monkeys can locate ripe fruits more efficiently when they are in groups than when they are solitary (Prescott *et al.*, 2005). Apparently, young monkeys benefit from the greater experience of adult monkeys, and thereby are better able to locate ripe nontoxic fruits.

Maternal and social influences on food selection should help young mammals overcome their neophobic response to foods that are consumed regularly by their mothers and fellow group members. As a corollary, young mammals should retain their neophobic response to foods normally avoided by adults. If the latter types of foods are toxic, then this social learning mechanism would serve as an indirect but effective way to help teach young animals about which foods to avoid (Galef and Clark, 1971).

Mechanisms for Tolerating Defensive Chemicals in Prey

Another strategy for coping with poisonous foods is to increase tolerance to them. Several physiological and behavioral tolerance mechanisms have been described.

Physiological tolerance mechanisms

One tolerance mechanism involves complexing ingested poisons with salivary proteins so as to inactivate them. This occurs, for instance, when tannins interact with specific types of proteins in the saliva (*e.g.*, proline-rich proteins, or PRPs). Salivary PRPs bind to tannins with high affinity

(Asquith *et al.*, 1987), and in so doing, increase palatability (Glendinning, 1992b) and reduce the toxicity (Mehansho *et al.*, 1987; Shimada, 2006; Shimada *et al.*, 2006) of tannin-containing foods. Many large herbivores produce salivary PRPs constitutively, but rodents must induce them over the course of several days of dietary exposure to tannins (Austin *et al.*, 1989; Mehansho *et al.*, 1992; Hagerman and Robbins, 1993; Shimada, 2006).

Another type of complexation occurs when animals ingest clay soils that have negatively charged cation-exchange sites (Johns, 1990). This ingestive behavior, called geophagy (or pica), is exhibited by numerous types of predator after ingestion of toxic foods (Kruegen, 1985; Johns, 1990; Klaus *et al.*, 1998; Krishnamani and Mahaney, 2000; Wilson, 2003). Because many poisons are positively charged in the acidic conditions of the stomach, they adsorb to the negatively charged cation-exchange sites in the clay soil and become inactivated. There are two lines of support for the hypothesis that geophagy is an adaptive response to ameliorate gastrointestinal malaise. First, when rats were experimentally poisoned or subjected to rotation-induced motion sickness, they avidly consumed clay soil or kaolin (a type of clay); control rats showed comparatively little consumption of those substances (Mitchell *et al.*, 1976; Morita *et al.*, 1988). Second, when Peruvian parrots were administered oral doses of a plant defensive compound (*e.g.*, quinidine) plus a preferred type of clay, they had 60% lower blood quinidine levels (3 h later) than did birds that were given quinidine without clay (Gilardi *et al.*, 1999). Future work is needed to identify the neural mechanisms that control expression of geophagy and the chemosensory mechanisms by which animals identify the soils with the highest cation-exchange capacity (Johns, 1990; Gilardi *et al.*, 1999).

Animals with a foregut fermentation chamber (*i.e.*, ruminants and kangaroos) increase their tolerance to some defensive chemicals by virtue of metabolic processes performed by their microbial flora. For example, goats in Hawaii can ingest the plant *Leucaena leucocephala* with impunity because they have a rumen bacterium (*Synergistes jonesii*) that metabolizes the toxic goiterogen [3-hydroxy-4(1H)-pyridone (DHP)], present in the plant's tissues (Jones and Megarrity, 1986; Allison *et al.*, 1992). Goats and steer in Australia lack this species of rumen bacterium and are poisoned by the *L. leucocephala* leaves. When cultures of bacteria from the rumen of Hawaiian goats are transferred to the rumen of Australian goats and steer, however, the animals become tolerant to *L. leucocephala* (Jones and Megarrity, 1986; Allison *et al.*, 1992). In fact, cultures of *S. jonesii* have been employed as inoculants elsewhere in the world to protect herds of livestock from DHP toxicity (Quirk *et al.*, 1988; Hammond *et al.*, 1989). Another example of ruminal detoxification involves the fermentation of oxalic acid by *Oxalobacter formigenes*. Livestock with this bacterium in their rumen can readily ingest forages (*e.g.*, halogeton) that

contain up 30% by weight of oxalate; those that lack this bacterium will die of oxalate toxicity soon after eating the same forage (James and Butcher, 1972; Allison *et al.*, 1985).

If ingested defensive chemicals elude inactivation by salivary proteins, clay soils, and rumen microbes, they then have the potential to cross the gastrointestinal epithelium and enter the general circulation. This movement is impeded, however, by the presence of detoxification enzymes (*e.g.*, cytochrome P450 3A, or CYP3A) and efflux transporters (*e.g.*, permeability-glycoprotein, or P-gp) in the gastrointestinal epithelium (Dearing *et al.*, 2005; Sorensen and Dearing, 2006). Both CYP3A and P-gp are known to reduce absorption of many orally administered drugs (Ayrton and Morgan, 2001; Funakoshi *et al.*, 2003; Dearing *et al.*, 2005). CYP3A metabolizes defensive chemicals as they pass through the epithelium, whereas P-gp actively transports them back into the gut lumen from the gastrointestinal epithelium. It is likely that differential expression of these two classes of protein contributes to species differences in gut permeability, and by extension, tolerance to defensive compounds such as α -pinene (Green *et al.*, 2004; Sorensen *et al.*, 2004) and cardiac glycosides (Marty, 1983). Parenthetically, it is notable that there are also high levels of cytochrome P450 detoxification enzymes expressed in the tissues lining the nasal cavity and lungs, which could rapidly degrade inhaled defensive compounds (Ling *et al.*, 2004; Castell *et al.*, 2005).

Finally, if defensive chemicals cross the gastrointestinal epithelium and enter the general circulation, they then encounter a diverse range of detoxification enzymes in the liver, kidneys, and to a lesser extent, the lungs, skin, testes, and thyroid gland. A detailed review of the detoxification process is beyond the scope of this paper (for reviews, see McLean and Duncan, 2006; Sorensen *et al.*, 2006). In brief, detoxification enzymes transform fat-soluble defensive chemicals into more water-soluble metabolites that can be excreted in urine or bile. There are two phases of the detoxification process. The first phase (called functionalization) involves oxidation, reduction, or hydrolysis reactions by P450 enzymes. Although functionalization usually makes defensive chemicals less toxic, it can act like a double-edged sword by converting defensive chemicals (*e.g.*, pyrrolizidine alkaloids) into more toxic intermediates (Fu *et al.*, 2004). The second phase (called conjugation) involves the addition of conjugates (*e.g.*, glucuronides, sulfates, or glutathione), which make the defensive chemicals, or their intermediates, highly polar and thus easy to excrete.

An important feature of detoxification enzymes is that their activity varies greatly across species and individuals within a species. For example, species differ in constitutive expression of specific detoxification enzymes (Watkins and Klaassen, 1986; Pass *et al.*, 2001), and these differences have been found to correlate with feeding ecology (Boyle *et*

al., 1999). Furthermore, the activity of any given detoxification enzyme can be increased or inhibited by the presence of defensive compounds in the diet (Pass *et al.*, 1999; Harris *et al.*, 2003). For instance, 36 h of repeated sampling from a nicotine diet can dramatically increase both P450 enzyme activity and tolerance to ingested nicotine (Snyder and Glendinning, 1996). Little is known, however, about how animals strike a balance between ingesting enough of a poison to perpetuate the induction process and not enough that they die.

Behavioral tolerance mechanisms

Predators can increase their tolerance to some chemically defended foods through behavioral means. One mechanism involves "processing" foods in ways that reduce the concentration of defensive chemicals. For example, meadow voles have been observed cutting branches off young conifers with their incisors, abandoning the branches for several days, and then returning later to consume the branches (Roy and Bergeron, 1990). Because the concentration of phenolics and tannins in the cut branches decays substantially over the course of several days, the authors inferred that the voles were manipulating the levels of defensive chemicals to increase palatability and reduce toxicity of this abundant food resource. Likewise, pikas manipulate the concentration of defensive compounds in their preferred vegetation by storing it in underground burrows and delaying eating it until the concentration of defensive chemicals has diminished below a critical level (Dearing, 1997).

A second behavioral tolerance mechanism involves switching frequently between different types of chemically defended prey (Freeland and Janzen, 1974). By feeding in this manner, predators could dilute the concentration of any one type of poison in the gut, and thereby avoid overwhelming any single detoxification pathway. Two recent reports provide support for this toxin dilution hypothesis. First, folivorous possums were healthier and ate more foliage when offered a mixed-foliage diet than a single-foliage diet (Wiggins *et al.*, 2006). Second, folivorous possums were offered one of two mixed-foliage diets: diet A consisted of two plant species, each of which contained defensive chemicals that activated different detoxification pathways; diet B also consisted of two plant species, but each contained defensive chemicals that activated the same detoxification pathway (Marsh *et al.*, 2006). The possums ate more diet A than diet B. Taken together, these findings indicate that generalist predators can increase intake (and minimize physiological harm) by switching among chemically defended prey that activate distinct detoxification pathways.

A third behavioral tolerance mechanism involves regulating intake of specific defensive chemicals so that they never exceed the threshold for toxicity. Several types of predators have been reported to feed in this manner, includ-

ing desert rats (Meyer and Karasov, 1989), birds (Brower and Calvert, 1985; Arellano-G. *et al.*, 1993; Jakubas *et al.*, 1993), and marsupials (Lawler *et al.*, 1998). Although the mechanistic basis for this regulatory process is poorly understood, one study (Lawler *et al.*, 1998) implicated a role of serotonin receptors. These receptors could occur in the visceral afferent fibers that project to the area postrema (AP) or in the AP itself (Saito *et al.*, 2003). Accordingly, ingestion of defensive compounds would stimulate release of serotonin. As the levels of serotonin increased, there would be a corresponding increase in the perceived magnitude of "gastrointestinal malaise." When it reached a threshold level, the animal would diminish intake of the defensive compound.

How Successful Are Predators at Coping With Defensive Chemicals in Their Prey?

From the foregoing discussion, it is clear that predators have evolved a prodigious array of chemosensory, toxicological, and behavioral mechanisms for detecting and coping with defensive compounds in prey. However, many of the examples discussed above were based on behavioral and physiological studies of captive animals. How well do these physiological and behavioral mechanisms function in nature?

While it is obvious that specialist predators such as koala bears can cope with the defensive chemicals in their *Eucalyptus* host plants (Moore and Foley, 2005), the capacity of generalist predators is less clear. Below, I discuss two well-documented examples of how generalist predators cope with chemically defended prey in their natural environment.

Example 1: Mice and overwintering monarchs

Each fall, the entire eastern population of monarch butterflies (*Danaus plexippus*) migrates to a few high-altitude overwintering sites in Mexico (Calvert and Brower, 1986). During the migration, the monarchs build up large fat reserves, constituting up to 50% of total body mass (Brower, 1985). At the overwintering sites, the monarchs form dense aggregations of tens of millions of individuals, which cover the trees, understory, and forest floor. These aggregations constitute a lipid-rich food bonanza for the local predators during the winter months, when calorically dense foods are scarce. The monarchs are not defenseless against predators, however. Their tissues are laced with cardiac glycosides (obtained from larval food plants) and pyrrolizidine alkaloids (obtained from adult nectar resources) (Seiber *et al.*, 1986; Kelley *et al.*, 1987).

Mark-recapture studies revealed that five species of mouse were abundant in the monarch overwintering sites, but only one (the black-eared mouse, *Peromyscus melanotis*) exploited the monarchs. This species recruited to the

monarch aggregations in large numbers, established stable territories, fed almost exclusively on the monarchs, and produced hundreds of offspring (Glendinning and Brower, 1990). Members of the other four species were occasionally live-trapped within the monarch aggregations, but they failed to establish territories or initiate winter reproduction.

After a role of competitive exclusion was eliminated (Glendinning and Brower, 1990), studies focused on the role of the monarch's defensive chemicals in determining why *P. melanotis* alone exploited the monarchs. Toxicological studies indicated that all of the rodent species were equally insensitive to the toxic effects of the cardiac glycosides and pyrrolizidine alkaloids (Marty, 1983; Glendinning *et al.*, 1990). What distinguished the five species of rodent was sensitivity to the bitter taste of the cardiac glycosides. *P. melanotis* individuals were significantly less sensitive than the other rodent species (Glendinning, 1990, 1992a). In addition, *P. melanotis* was the only species that learned how to "un-zip" the abdomen and extract the abdominal contents, which contained relatively low levels of cardiac glycosides (Glendinning, 1990, 1993). These findings reveal that nearly an entire community of predators was "fooled" by a false signal—*i.e.*, a bitter taste that did not betoken toxicity. *Peromyscus melanotis* individuals alone were able to breach the monarch's chemical defenses and substantially increase their reproductive fitness.

Example 2: Free-ranging livestock and toxic plants

About 50% of the land surface on our planet is devoted to grazing livestock (James *et al.*, 1992). In many areas, the livestock roam over wide expanses of land and encounter a diverse range of plant species. A major source of mortality to these animals is the consumption of poisonous rangeland plants. Annual rates of mortality to poisoning range from 2% to 5% over the entire western United States (James *et al.*, 1992), but can reach levels as high as 13% in specific areas (Pfister *et al.*, 2003). The impact of poisonous plants cannot be measured solely in terms of outright deaths, because many poisons produce more subtle effects; for example, they stunt growth, interfere with reproduction, impair cognition, or cause lethargy, weight loss, and depilation (Fowler, 1983). Ingestion of toxic plants can also harm developing fetuses, resulting in malformation, early parturition, abortion, or death (Panter *et al.*, 1992).

The explanation for why rangeland livestock voluntarily consume large quantities of poisonous plants cannot be attributed to a single factor. To illustrate the complexity of the situation, I will discuss three common types of plant poisoning in the western United States. One type involves a plant called larkspur (*Delphinium spp.*). The effect of larkspur consumption can be catastrophic, causing 13% mortality in a large herd of cattle (Pfister *et al.*, 2003). Several factors contribute to larkspur poisoning. The plant is highly

palatable, produces an acute toxicity (*i.e.*, death within 2–8 h), and generates a relatively weak conditioned feeding aversion (CFA) (Ralphs *et al.*, 1988, 1990). In addition, there is evidence that the positive effect of conspecifics eating larkspur (*i.e.*, social facilitation) can over-ride a previously conditioned feeding aversion to larkspur (Ralphs and Olsen, 1992).

A second type of poisoning involves locoweed (*Oxytropis* and *Astragalus spp.*). This plant is frequently over-consumed by horses, cattle, and sheep, generating a variety of symptoms—emaciation, weakness, poor coordination, muscular trembling, and visual impairment (Adcock and Keiss, 1969; James *et al.*, 1969; Molyneux and Ralphs, 1992). When frightened, a "locoed" animal will flee aimlessly, crashing into trees or logs. Two factors contribute to locoweed poisoning. First, even though species of locoweed vary considerably in palatability, they are all toxic (Ralphs and Olsen, 1987). This observation indicates that the chemosensory and/or somatosensory features of locoweed that determine palatability vary independently from those that determine toxicity. Second, even though animals can develop conditioned feeding aversions to locoweed under controlled captive conditions, animals in the field have been observed ingesting locoweed even after showing obvious toxic symptoms (Molyneux and Ralphs, 1992). One might infer that this seemingly maladaptive ingestive behavior is a by-product of the domestication process, but it is notable that free-ranging elk (*Cervus elaphus nelsoni*) also consume locoweed and become "locoed" (Wolfe and Lance, 1984).

A final type of poisoning involves plants that contain pyrrolizidine alkaloids (PAs) (*e.g.*, *Senecio* and *Crotalaria spp.*). As noted earlier, PAs are not inherently toxic. It is the metabolites of the detoxification process that are toxic. Prolonged exposure to these metabolites causes a progressive hepatotoxicity, which often takes 12–18 months to develop (Mattocks, 1971; Hooper, 1978; Fu *et al.*, 2004). Two factors contribute to the high rates of mortality from over-consuming PA-containing plants (Molyneux and Ralphs, 1992). Most species are highly palatable to livestock, and consumption of PA-containing plants does not appear to generate postingestive malaise (Molyneux and Ralphs, 1992).

Why Do Generalist Predators Have Trouble Coping With Chemically Defended Prey?

If generalist predators have so many adaptations for assessing the potential toxicity of chemically defended prey, then why do so many err with monarch butterflies and rangeland plants? The simple answer is that the responses to monarchs and rangeland plants are anomalous, and that predators usually display more adaptive responses to chemically defended prey. In the absence of additional information, one cannot exclude this possibility. However, it is

more likely that the problems predators encounter with monarchs and rangeland plants reflect broader challenges that predators face with all chemically defended prey. These challenges fall into four broad categories.

The first is that there is no simple relationship between palatability and toxicity. This relationship was originally inferred based on the observation that many naturally occurring poisons taste bitter to humans (Bate-Smith, 1972; Garcia and Hankins, 1975). More recent work indicates that the bitterness/toxicity relationship is more complex than previously thought. For instance, while most naturally occurring poisons taste bitter, the opposite is not true; that is, many bitter-tasting compounds are nontoxic (Brower, 1984; Brieskorn, 1990; Glendinning, 1994). In addition, the threshold concentration for toxicity appears to vary independently of the threshold concentration for orosensory aversiveness (Cottee *et al.*, 1988; Glendinning, 1994; Pass and Foley, 2000). Taken together, these observations indicate that even though bitterness can signal toxicity, it does not provide reliable information upon which to base a decision about whether a food is "safe."

The second challenge is that even though many of the foods that elicit emesis, nausea, or generalized malaise also condition a feeding aversion (Parker, 2006), there are many exceptions (*e.g.*, larkspur, locoweed, and PA-containing plants). The situation is further complicated by the fact that ingestion of rewarding drugs (*e.g.*, amphetamine and morphine) can also condition a feeding aversion (Gamzu, 1977). This latter observation led Gamzu (1977) to speculate that feeding aversions may be conditioned by any food that produces a sudden change in physiological or psychological state, irrespective of whether the change is positive or negative.

The third challenge stems from the fact that many natural habitats contain a bewildering variety of prey species that vary in palatability, toxicity, and availability. Under these conditions, the ability to associate postingestive malaise with a particular food is difficult, particularly if the predator ingests multiple types of prey during a meal (Zahorik *et al.*, 1990; Duncan and Young, 2002). In addition, predators are often forced to shift among different habitats to track changes in food availability. This habitat-shifting poses challenges because the predators must cope with a new and potentially toxic array of prey species in each habitat. Indeed, there is evidence that poisonings are more common immediately after predators have entered a new habitat (Provenza *et al.*, 1992).

The fourth challenge is that some plant tissues contain pharmacologically or medicinally active compounds. Although it is well established that humans exploit these compounds, the extent to which other mammal species do so is less clear (Huffman, 2003). There are numerous reports of wild animals avidly consuming pharmacologically active plant tissues and then exhibiting behaviors that are

indicative of intoxication (Siegel, 1989). Further, there are reports of predators consuming bitter and medicinally active plant compounds after becoming sick in the wild (Koshimizu *et al.*, 1994; Huffman, 1997; Huffman *et al.*, 1998) or in captivity (Vitazkova *et al.*, 2001). These observations raise a number of intriguing questions. How widespread are these apparent examples of zoopharmacognosy and self-medication? Are sick predators more likely than healthy ones to consume bitter plant tissues? If so, how do predators discriminate between bitter plant tissues that are toxic and those that are pharmacologically or medicinally active?

Conclusions

Predators possess a diversity of adaptations for coping with chemically defended prey. These adaptations involve integrated physiological and behavioral mechanisms for detecting, detoxifying, and breaching chemical defenses. At this point, we know little about how effectively these mechanisms function in nature. The examples involving monarch butterflies and rangeland plants indicate that predators often err when assessing the dangers posed by chemically defended prey. Future studies should explore this possibility in greater detail with free-ranging predators. Another important subject to explore would be species differences in capacity to cope with chemically defended prey. To this end it would be instructive to compare predators that rarely encounter chemically defended prey (*e.g.*, carnivores) with those that often encounter such prey (*e.g.*, insectivores and herbivores). One would expect the latter class of predators to express a more extensive repertoire of mechanisms for coping with and tolerating defensive chemicals (Jacobs *et al.*, 1978; Glendinning, 1994; Iason and Villalba, 2006; Parker, 2006).

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