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COSTS OF EXPLOITING POISONOUS PREY: EVOLUTIONARY TRADE-OFFS IN A PREDATOR-PREY ARMS RACE

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Abstract.—Evolutionary trade-offs often are expected to arise between traits that share similar functions or resources. Such costs are well known from a variety of coevolutionary systems, but examples are conspicuously absent from predator-prey interactions. We present evidence of a trade-off between two disparate functions—predatory and antipredatory ability—in a species of garter snake that has evolved resistance to the neurotoxin of its prey. Patterns of among-family variation suggest a genetic basis to the trade-off. Both resistant and nonresistant populations of snakes exhibit the trade-off, suggesting that it stems from a fundamental aspect of organismal performance. This cost may help to explain the geographic mosaic of predator exploitative ability and prey defense that exists in this system.

Key words.—Coevolution, garter snake, resistance, tetrodotoxin, toxicity.

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Costs of adaptation are a basic tenet of evolutionary thinking from life-history theory (Roff 1992) to models of coevolution (Roughgarden 1983; Thompson 1994). Such trade-offs may arise because of an economic limitation wherein resources allocated to one structure or function are not available for others (Simms 1992; Zangerl and Bazzaz 1992; Thompson 1994) or because specialization of a feature leaves it less able to perform a variety of tasks (a jack-of-all-trades is a master of none; Futuyma and Moreno 1988; Thompson 1994).

The importance of trade-offs in models of evolution arises because the ultimate cost, reduced fitness, generates a constraint to evolutionary change. Recent evaluations of the prevalence of costs of adaptation have concentrated on identifying systems wherein trade-offs with fitness have been demonstrated (e.g., Reznick 1985; Bergelson and Purrington 1996). Although it is essential to evaluate existence of costs in terms of fitness consequences, this approach does not always reveal phenotypic characters whose evolution is affected. All trade-offs, whether a result of ecological specialization or resource allocation, must stem directly from a compromise at the phenotypic level. For example, ecological trade-offs may arise when a defensive compound that is effective against one species does not work against others (e.g., Berenbaum et al. 1986; Simms 1992). When allocation trade-offs occur, resources used to produce one structure are unavailable to make another (Berenbaum et al. 1986; Simms 1992; Zangerl and Bazzaz 1992; Bergelson and Purrington 1996). One common observation in plant-herbivore systems is a negative correlation between plant defense and some measure of biomass or reproductive success (Simms 1992; Zangerl and Bazzaz 1992), usually without identification of the specific trait that is compromised through defense. Perhaps most surprisingly, costs of adaptation are not always evident (Simms 1992; Bergelson and Purrington 1996), and their ubiquity is still a matter of contention.

Some of the most extreme adaptations result from antagonistic coevolution. Adaptation by one species generates selection on its partner to adapt and vice versa, creating an escalating "arms race" of counter-adaptation. Arms races center on a phenotypic interface comprised of traits that mediate interactions between species. As arms races proceed, the traits at the interface become more and more exaggerated in each species, and trade-offs in performance under alternative selective pressures are expected to arise. Theoretical models suggest that coevolutionary interactions between victim and exploiter need not continue in an ever increasing escalation, but instead might enter a variety of cyclical chase dynamics. The form of such chases and the stability of the victim-exploiter system depends on the existence and nature of costs associated with the phenotypic interface (Saloneimi 1993; Abrams and Matsuda 1996; Gavrilets 1997). This information is currently unavailable for natural predator-prey systems (Abrams and Matsuda 1996).

From a microevolutionary perspective, one of the best documented predator-prey systems includes the newt *Taricha granulosa* and its predator, the garter snake, *Thamnophis sirtalis,* in the Pacific Northwest of North America (Brodie and Brodie 1990, 1991, 1999). Newts of the genus *Taricha* produce tetrodotoxin (TTX) from glands in their skin (Mosher et al. 1964; Wakely et al. 1966; Brodie 1968; Brodie et al. 1974; Daly et al. 1987). TTX is an extremely potent neurotoxin that acts as a Na^+ channel blocker. Although all members of the genus possess this toxin, *T. granulosa* is many times more toxic than any other species. One adult newt produces enough toxin to kill up to 25,000 white mice, or approximately seven humans (Brodie et al. 1974). The only predator known to forage on newts and resist the effects of this toxin is the garter snake, *T. sirtalis.* Within populations, resistance to TTX varies among individual snakes and has a heritable basis (Brodie and Brodie 1990). Resistance is not affected by either short-term or long-term exposure to TTX

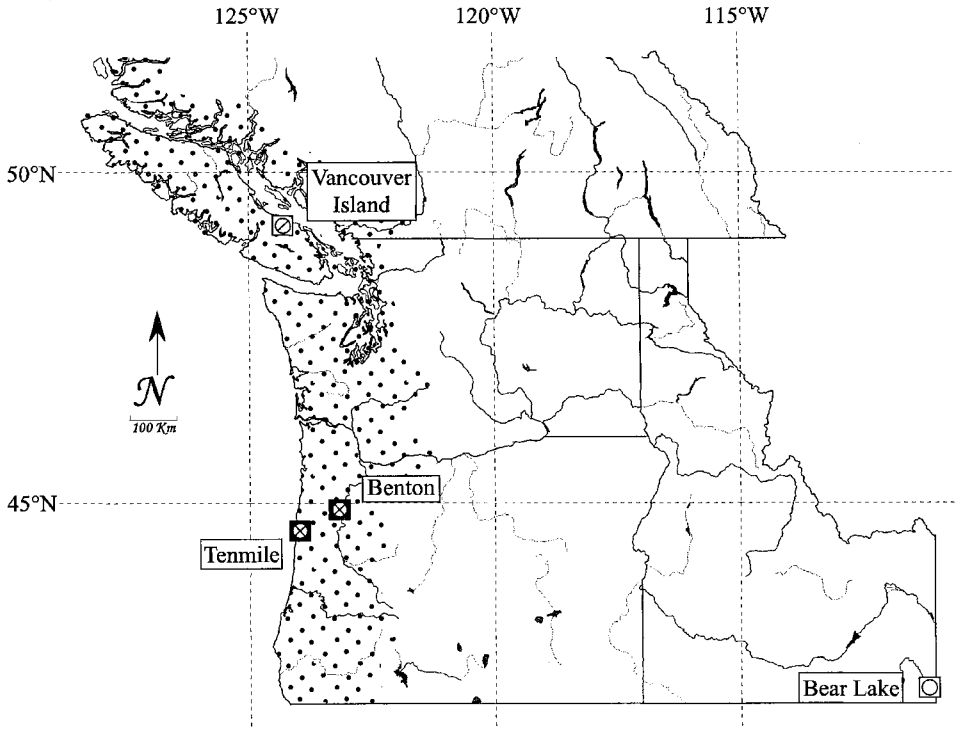

FIG. 1. Geographic distribution of garter snake resistance and newt toxicity in the North American Pacific Northwest. The range of newts is indicated by the stippled area. Populations of garter snakes studied are indicated by a box (filled boxes indicate populations resistant to TTX, open boxes indicate populations that are nonresistant). Populations of newts are indicated by circles within the boxes (open circles indicate no newts present, circles with a slash indicate newt populations that lack TTX, circles with an X indicate populations with TTX; data from Brodie and Brodie 1990, 1991).

(Brodie and Brodie 1991; Ridenhour et al. 1999), so maternal effects are unlikely to explain familial differences. Among populations, the levels of both newt toxicity and snake resistance are variable but roughly matched (Brodie and Brodie 1990, 1991, 1999; Fig. 1), representing a geographic mosaic of coevolutionary outcomes (Thompson 1994). Garter snake populations allopatric with these newts are not resistant to TTX, whereas sympatric populations are resistant (Brodie and Brodie 1990). Island populations of *T. granulosa* from British Columbia apparently lack TTX, and garter snakes from these populations are nonresistant (Brodie and Brodie 1991). Other garter snakes that co-occur with *Taricha* are susceptible to TTX (Brodie 1968; Brodie and Brodie 1990), which supports the view that resistance to TTX is an extreme adaptation by a predator to its toxic prey.

Using a bioassay to detect individual differences in susceptibility to TTX, we investigated whether resistance and locomotor performance were negatively associated, thereby representing a trade-off between predatory and antipredatory abilities of garter snakes. Families of garter snakes were examined to determine whether the observed relationship had a genetic basis. We replicated our investigation in one nonresistant population and two resistant populations of garter snakes to assess the generality of the trade-off in this predator-prey system.

METHODS

We examined three populations of garter snakes with known levels of resistance (Fig. 1; Brodie and Brodie 1990). Two populations from Oregon ("Tenmile" from Tenmile Creek, Lane Co., OR, and "Benton" from Benton Co., OR) are sympatric with *T. granulosa* and are approximately one order of magnitude more resistant to TTX than the population from Idaho ("Bear Lake" from Bear Lake, Co., ID), which is outside the range of *Taricha*. Although the Bear Lake population is referred to as "nonresistant," all three populations exhibit individual variation in susceptibility to TTX and heritability of this variation has been established for the Tenmile population (Brodie and Brodie 1990).

Speed and resistance were assayed on neonate snakes born in the laboratory to wild-caught females. A total of 734 snakes from 65 families were sampled (Tenmile: 430 snakes from 33 families; Benton: 103 snakes from 13 families; Bear Lake: 201 snakes from 19 families). Snakes were housed individually during the experiment, watered daily, and were not fed until testing was completed. All subjects were tested between three and 10 days of age, and trials were conducted at 25–26°C.

We scored resistance to TTX using a bioassay based on whole organism performance (Brodie and Brodie 1990). Each individual snake was raced on a 2-m linear track and the

maximum 0.5-m speed in a trial was taken as the sprint speed score. Tenmile and Benton populations were hand timed with a stopwatch, whereas the Bear Lake population was tested on an identically designed track that was equipped with infrared sensors to electronically time sprint speed (see Brodie and Brodie 1990). Individuals were tested repeatedly and the mean of all scores was taken as an individual's baseline speed. Snakes from Tenmile and Benton were tested twice on two successive days for a total of four repeated measures, whereas snakes from Bear Lake were tested twice on the same day. Twenty hours after the last sprint test, neonates were given intraperitoneal injections of TTX. Thirty minutes after injection, snakes were tested again to obtain a measure of postinjection speed. Repeated measures of postinjection speed were taken at 48-h intervals (three measures for Tenmile and Benton, two for Bear Lake). Again, the average of repeated trials was taken as an individual's measure of postinjection speed. Resistance was scored as the percentage of an individual's baseline speed crawled after injection (postinjection speed/baseline speed). Individuals that are greatly impaired by TTX crawl at only a small proportion of their normal speed, whereas those that are unaffected by an injection of TTX crawl at 100% of their baseline speed. The bioassay is highly repeatable and enables us to assess individual differences in susceptibility to TTX (Brodie and Brodie 1990, 1991). The two resistant populations were tested after injections of 0.001 mg TTX, and the nonresistant Bear Lake population was tested after injections of 0.00005 mg TTX. These doses result in an average reduction of speed to approximately 50–70% of baseline speed in the respective populations.

The usual approach to testing trade-offs is to examine correlations between salient variables within a population. Because speed is included in our bioassay of resistance, correlations between these traits might reflect a statistical artifact. Therefore, we investigated the existence of trade-offs by regressing postinjection speed on baseline speed and examining the slope of the relationship. If TTX affects all individuals equally, then the slope of the regression will be one, and the effect of TTX is purely additive and reflected in the intercept. If, however, the effect of TTX is dependent on the speed of an individual, then the slope should differ from one: a slope of less than one indicates a trade-off wherein the fastest individuals have low resistance, whereas a slope of greater than one indicates that faster individuals have greater resistance. This regression was calculated separately for each population, using the following model: postinjection speed = $\alpha + \beta$ (baseline speed) + ϵ. All statistical analyses were performed using JMP version 3.01.

To assess phenotypic and genetic evidence for trade-offs, we performed regressions on individual values as well as on family means. Family-mean correlations can be used to approximate genetic correlations among traits, especially when family sizes are large (cf. Arnold 1981; Via 1984). In this study we use an analogous approach to infer a genetic basis of the relationships among characters. Our samples are presumed to represent full-sib families, so the regression of postinjection speed on baseline speed may result from dominance effects and maternal effects and should not be viewed as a direct estimate of the additive genetic covariance.

TABLE 1. Regression slopes (b) of postinjection speed on baseline speed.

Population	Individual values	Family means
Tenmile	n = 430	n = 33
Unadjusted	b = 0.460	b = 0.514
	t = −12.16***	t = −2.65*
Mass-adjusted	b = 0.404	b = 0.358
	t = −12.59***	t = −3.36**
Benton	n = 103	n = 13
Unadjusted	b = 0.514	b = 0.510
	t = −6.03***	t = −4.67***
Mass-adjusted	b = 0.433	b = 0.390
	t = −5.68***	t = −3.24***
Bear Lake	n = 201	n = 19
Unadjusted	b = 0.440	b = 0.654
	t = −5.47***	t = −0.69
Mass-adjusted	b = 0.147	b = 0.127
	t = −9.65***	t = −2.52*

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Body size is known to covary positively with speed in *T. sirtalis* (Brodie and Brodie 1990) and with locomotor performance in snakes in general. To determine whether body size also was related to resistance, we repeated the regression analysis using mass-adjusted measures of postinjection and baseline speed. Each variable was regressed on neonate mass and the residuals used as a mass-adjusted measure. This adjustment was performed separately for each variable in each population. If body size contributes to TTX resistance through some sort of dilution effect (i.e., larger snakes are more resistant), the slope of the mass-adjusted regression of postinjection speed on baseline speed should differ from the unadjusted slope.

RESULTS

The regressions of postinjection speed on baseline speed indicated the existence of a trade-off in all populations. In each population, the slope of this regression was significantly less than one, indicating that the slowest snakes were the most resistant (Table 1, Fig. 2). This relationship held true when family means are investigated for the two resistant populations (Table 1, Fig. 3). The slope of the relationship between family means did not differ from one in the Bear Lake population (but neither was this relationship different from zero, suggesting low power for the test).

When postinjection speed and baseline speed were adjusted for mass differences among individuals, the phenotypic trade-off was still evident in all populations (Table 1). The mass-adjusted slope of the relationship was similar to the unadjusted slope in both resistant populations, but differed considerably in the nonresistant Bear Lake population. Although this difference in slopes was not significant in the Bear Lake population (t = 1.593, df = 200, P = ns), it did suggest that mass was related to resistance in a way different from the resistant populations. All mass-adjusted slopes of family-mean regressions were significantly less than one.

DISCUSSION

As predators, *T. sirtalis* depend on resistance to TTX to exploit newts as a prey resource. As prey, speed is an essential

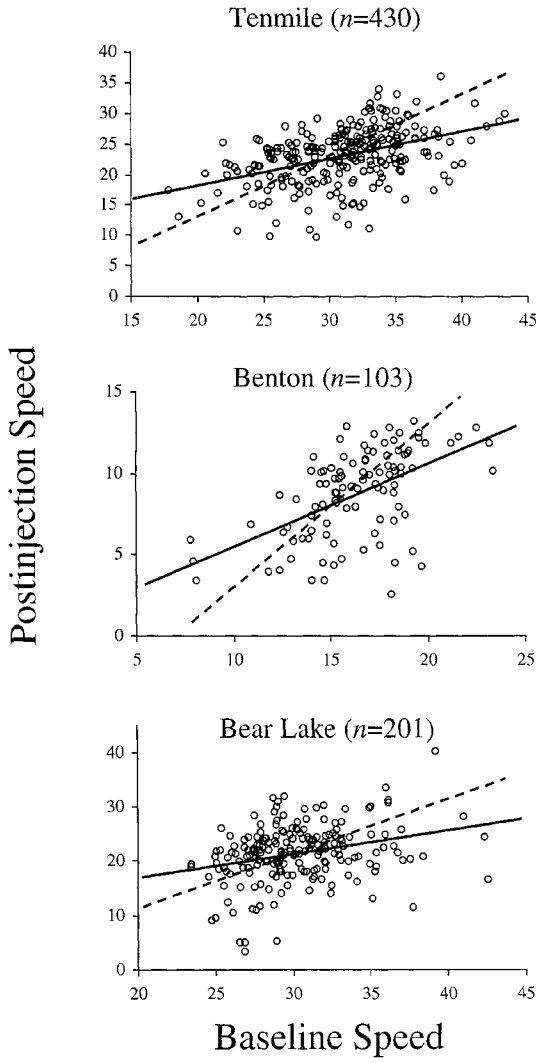

FIG. 2. Regressions of postinjection speed on baseline speed. For each population, the slope of the regression is significantly less than the expected slope of one (shown as dashed line). See Table 1 for regression slopes and significance tests.

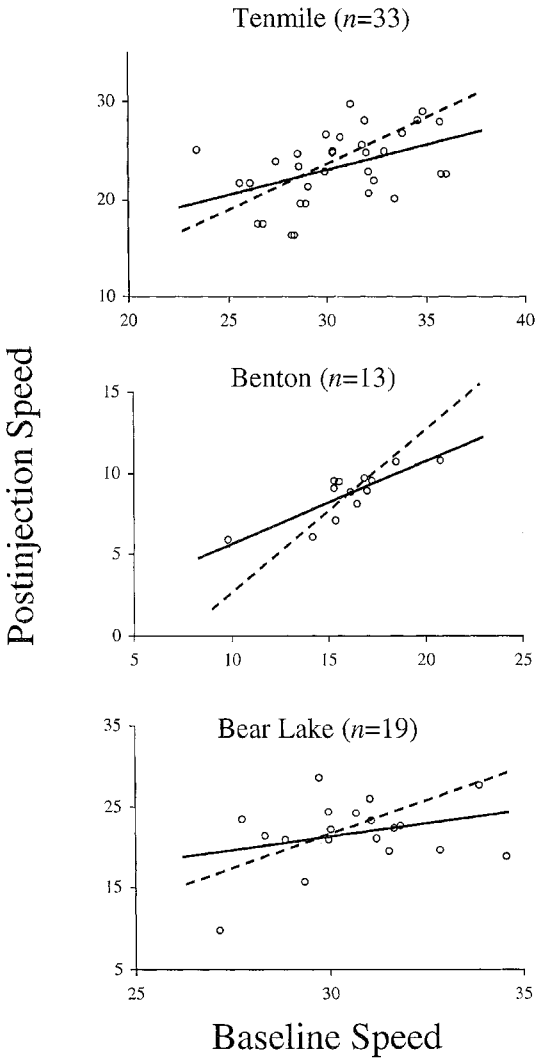

FIG. 3. Family-mean regressions of postinjection speed on baseline speed. The slope of the regression is significantly less than the expected slope of one (shown as dashed line) in both the Tenmile and Benton populations. See Table 1 for regression slopes and significance tests.

escape behavior that is known to influence survival in this species (Jayne and Bennett 1990). The trade-off between these traits is especially surprising because it occurs between predatory and antipredatory abilities, rather than between functionally related characters. If allocation theory explains the existence of this cost, then there must be some common resource that is shared by both resistance and speed. The phenotypic source of this covariance may lie in the physiological basis of TTX resistance.

The mechanism of TTX resistance in garter snakes is still unknown, but the most likely possibility is the existence of TTX-resistant Na^+ channels in nerves and/or muscles of resistant animals. TTX binds to Na^+ channels in muscles and nerves and blocks action potentials. Na^+ channels are encoded by a multigene family and different forms of Na^+ channels have different affinities for TTX (Yoshida 1994; Sangemeswaran et al. 1996; Chen et al. 1997; Kaneko et al. 1997); TTX-resistant channels have been found in many species (Caldwell and Milton 1988; Yoshida 1994; Sangemeswaran et al. 1996; Chen et al. 1997; Kaneko et al. 1997). Both TTX-resistant and TTX-sensitive Na^+ channels are expressed in neonatal rat myoblasts and myotubes, where TTX-resistant channels are initially more common; however, at six days the proportion of TTX-sensitive channels increases until in adult muscle the TTX-sensitive channel is predominant (Weiss and Horn 1986a, 1986b). These TTX-resistant channels exhibit lower conductance and slower kinetics than other Na^+ channels (Pappone 1980; Weiss and Horn 1986a, 1986b; Campbell 1992; Yoshida 1994). It is unclear whether these physiological differences translate directly to altered organ-

ismal performance. If the mechanism of TTX resistance in garter snakes involves the evolution of TTX-insensitive channels, then the trade-off between resistance and speed in resistant snake populations might stem from the altered function of such Na^+ channels. This seems to be a plausible scenario: The existence of TTX-resistant channels in garter snakes might be explained through the neotenic retention of channel expression with these properties from early development. This mechanistic hypothesis could explain the unexpected trade-off between different ends of the predation spectrum because specialization of neural physiology for resistance could compromise locomotor ability.

Family-mean regressions suggest a genetic basis to the trade-off (Fig. 3), although our data represent full-sib families and may include components of dominance variance and common family environments. However, TTX resistance is not inducible in either short-term (Brodie and Brodie 1990) or long-term (Ridenhour et al. 1999) experiments, so maternal effects working through exposure to TTX are unlikely to affect TTX resistance. Both resistant and nonresistant populations of garter snakes exhibit the trade-off, further suggesting that a fundamental aspect of organismal performance drives resistance. Snakes from Bear Lake are not resistant at a level that would allow them to feed on toxic newts, but they nonetheless exhibit variation in their susceptibility to TTX that covaries with speed.

Body size appears to be related to resistance in the nonresistant population, but not in resistant ones. When the effects of mass were removed from the regression of postinjection speed on baseline speed, the slope was decreased in the Bear Lake population (although not significantly so). This effect is consistent with a stronger influence of body size on postinjection speed than on baseline speed, as is expected if body size affects resistance. Larger snakes may be better able to withstand the effects of toxin simply because of a dilution effect. Snakes from resistant populations do not exhibit a relationship between resistance and size, possibly because their absolute level of resistance is too high for a dilution effect to contribute to variation among individuals.

Despite their theoretical importance and presumed prevalence, trade-offs are often not observed. This absence has led to a variety of hypotheses regarding the types of costs in natural systems and the best ways to detect them. The chief distinctions between types of costs are those that arise from resource allocation to different features or functions and those that arise from competing aspects of ecological performance (Simms 1992). The trade-off between TTX resistance and speed demonstrates the blurred line that separates these categories. The negative relationship between these traits likely results from some sort of resource limitation, perhaps the compromised Na^+ channel function suggested above, yet the presumed fitness consequences of the trade-off must result from compromises between two disparate aspects of ecological performance—predatory and antipredatory ability. Of course, this apparent fitness trade-off might be mediated by other traits, so the importance of such costs must be evaluated under natural conditions (e.g., Mauricio 1998).

Whatever their source, the existence of trade-offs may help to explain the interpopulational variation in exploitative ability and defense that is present in the snake-newt system (Fig. 1) and that is commonly observed in other coevolutionary interactions. The geographic mosaic view of coevolution recognizes that interactions take place at the population level and that the nature of an interaction may vary depending on details such as mutation rate, selection pressures, and phylogenetic history, that are specific to each population (Thompson 1994). The resulting geographic pattern may appear as coevolution in some populations, but not in others. Costs of adaptation may promote this pattern of geographic variation because of the concomitant fitness consequences. For example, if there were no cost to resistance, snakes that invade a new area inhabited by nontoxic prey might retain their resistance, generating a geographic pattern of resistance and toxicity that would appear inconsistent with coevolution. In the absence of continued selection by prey, the cost of resistance should lead to the loss of resistance, so that toxicity of prey and resistance of predators will match among sympatric populations. Whether this scenario holds for the geographic mosaic in the snake-newt system will be determined by investigations of the biogeographic history of the two species now underway.

For garter snakes, the evolutionary consequence of exploiting toxic prey is that they have themselves become more vulnerable prey. Whatever the proximate explanation for this trade-off, it is critical to maintaining a coevolutionary arms race between two coevolving species. Without a cost to the adaptations that allow one species to exploit the other, one would expect rapid evolution and a resulting winner of the arms race (e.g., Gavrilets 1997). For example, if snake resistance had no cost, we might expect all sympatric populations to become fully resistant to prey toxins. Toxic prey then no longer have an advantage and the coevolutionary interaction ceases, ending with mildly toxic prey and superresistant predators. The extreme level of resistance by predator and toxicity of the prey, along with the matched level of both traits in sympatric populations, suggests that these species are indeed caught in lock-step coevolution.

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