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"PharmEcology: A pharmacological approach to understanding plant-herbivore interactions: an introduction to the symposium"

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Synopsis A central goal in understanding the ecology and evolution of animals is to identify factors that constrain or expand breadth of diet. Selection of diet in many animals is often constrained by chemical deterrents (i.e., secondary metabolites) in available food items. The integration of chemistry and ecology has led to a significant understanding of the chemical complexity of prey (e.g., animals, plants, and algae) and the resultant foraging behavior of consumers. However, most of the literature on chemical defenses of marine and terrestrial prey lacks a mechanistic understanding of how consumers tolerate, or avoid, chemically-defended foods. In order to understand ecological patterns of foraging and co-evolutionary relationships between prey and consumers, we must advance our understanding of the physiological mechanisms responsible for chemical interactions. Such mechanistic studies require the integration of the discipline of pharmacology with ecology, which we call "PharmEcology." Pharmacology provides the tools and insight to investigate the fate (what the body does to a chemical) and action (what a chemical does to the body) of chemicals in living organisms, whereas ecology provides the insight into the interactions between organisms (e.g., herbivores) and their environment (e.g., plants). Although, the general concepts of pharmacology were introduced to ecologists studying plant–herbivore interactions over 30 years ago, the empirical use of pharmacology to understand mechanisms of chemical interactions has remained limited. Moreover, many of the recent biochemical, molecular and technical advances in pharmacology have yet to be utilized by ecologists. The PharmEcology symposium held at a meeting of the Society for Integrative and Comparative Biology in January of 2009 was developed to define novel research directions at the interface of pharmacology and ecology.

Introduction

Understanding the mechanisms and reach of interactions between plants and animals has been an important goal in ecology and evolutionary biology. For example, insights into the fundamental concepts and mechanisms of co-evolution have arisen from studies of interactions between herbivores and plants (Berenbaum 1983; Thompson 2005; Wheat et al. 2007). These discoveries have been obtained by integrating the sub-disciplines of nutritional, behavioral, physiological, and chemical ecology and have revealed how plants deter herbivores through physical and chemical defenses and how herbivores overcome these defenses through behavioral, physiological and biochemical adaptations. No single sub-discipline can provide the insight that is needed to fully understand plant–herbivore interactions. However, given the broad use of chemical defenses in plants, chemical ecology has played a significant role in advancing the field of plant–herbivore interactions (Freeland 1991; Rosenthal and Berenbaum 1992; Paul et al. 2007; Amsler 2008).

Ecologists willing to embrace and apply chemistry have begun to identify both the patterns of chemical interactions and some of the mechanisms that maintain, or perturb, those interactions. Initial studies which were directed towards broad groups of compounds such as tannins, have given way to more focused work on characterizing compounds with known modes of action and which are demonstrably important for free-ranging animals (Moore and Foley 2005). Even so, it is apparent that understanding the chemical mediators of interactions is not sufficient to predict the outcome. Chemical ecology therefore also relies on integrating other sub-disciplines to understand how herbivores respond to chemical defenses. For example, physiological studies have shown that chemicals in plants can affect a wide range of homeostatic processes in the

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body such as acid–base balance (Foley et al. 1995), water balance (Dearing et al. 2002) and energy partitioning (Sorensen et al. 2005b). These effects have to be monitored and integrated with other signals that regulate food intake so that animals do not become poisoned, and thus require insight into behavioral ecology. For example, behavioral changes in size of meal or in intervals between meals (Sorensen et al. 2005a; Wiggins et al. 2006; Marsh et al. 2007; Torregrossa and Dearing 2009) or in selection of diet explain how animals manipulate the rate at which toxins are consumed and accumulate in the body.

PharmEcology

The PharmEcology symposium focused on the emergent integration of yet another sub-discipline into the field of plant–herbivore interactions—pharmacology. Pharmacology is the "study of drugs, their sources, their nature and properties" (Dictionary 2007). Similarly, many ecologists studying chemical interactions between prey and consumers focus on the sources of secondary metabolites (SMs, i.e., which plants have them and which ones do not), their nature (isolation, identification, and quantification of SMs) and their properties (how they affect consumers' behavior and physiology). Pharmacology can therefore provide a logical framework to fully integrate chemical, physiological, behavioral, and nutritional interactions between prey and consumers. Some ecologists have embraced aspects of pharmacology to explain biochemical interactions between plants and herbivores. For example, DNA cloning and pharmacogenomics have been applied by ecologists to identify a link between the expression of metabolizing enzymes and foraging behavior of herbivores (Li et al. 2004; Skopec et al. 2007). However, the concepts and techniques of pharmacology have not been utilized to their full potential by ecologists, in part, because of lack of training and because of lack of communication between disciplines.

The term "*PharmEcology*" has been coined to describe efforts that aim to understand plant–herbivore interactions using pharmacological principles and techniques. Although the majority of progress in this area focuses on plant–herbivore interactions, the concepts of PharmEcology apply to all chemical interactions between prey (e.g., plants, algae, animals) and consumers. PharmEcology draws from the overlap between drug–human interactions and SM–consumer interactions. Synthetic chemists and prey both can synthesize chemicals that are absorbed and bind with specific receptors, thus eliciting behavioral or physiological responses. The difference between industry's chemists and nature's chemists is that prey have had millions of years of evolution to develop chemically diverse defenses against a range of attackers, that include microbes, consumers, and conspecifics. Industrial chemists typically have limited diversity in their chemical products and aim to synthesize chemicals that interact with a single target in humans. There is also significant overlap in how humans and consumers process ingested chemicals (e.g., drugs or SMs). In general, the bodies of all animals, be they human patients or wild herbivores, are designed to minimize concentrations and thus toxicity from ingested chemicals. Nearly all chemicals that are consumed undergo some level of absorption, distribution, metabolism, and excretion, together referred to as "ADME" (Sorensen et al. 2006). Although mechanisms of ADME are generally shared across taxa, the endpoint of these processes may differ. Herbivores and other consumers should minimize the potential for toxicity through lowered absorption and enhanced metabolism and elimination of SMs. In contrast, the aim of drug therapy in human patients is to maintain therapeutic concentrations at the target site (i.e., effective absorption and distribution together with slow metabolism and elimination).

History of PharmEcology

Given the overlap between drug–human interactions and prey–consumer interactions, advances in pharmacology can provide a useful and expansive toolbox for ecologists. To date, ecologists have exploited only a subset of the available pharmacological tools. Historically, the application of pharmacological advances by ecologists has lagged significantly behind their routine use in pharmacology (Fig. 1). For example, *in vivo* studies that measure the concentration-time profile of chemicals in the body (i.e., pharmacokinetics, PK) to assess ADME capacity was well described by pharmacologists in the 1930s (Gibaldi and Perrier 1982), but ecologists did not utilize this approach until 2003 (Sorensen and Dearing 2003; Boyle and McLean 2004). Although *in vitro* tests of metabolizing enzymes were routine in pharmacology by the 1950s (Bachmann and Bickel 1985), ecologists did not apply this technique until the early 1970s (Krieger et al. 1971). Studies of metabolism continued to be dominated by ecologists investigating terrestrial insect herbivores despite Freeland and Janzen (1974) bringing the concepts of pharmacology to ecologists working on mammalian

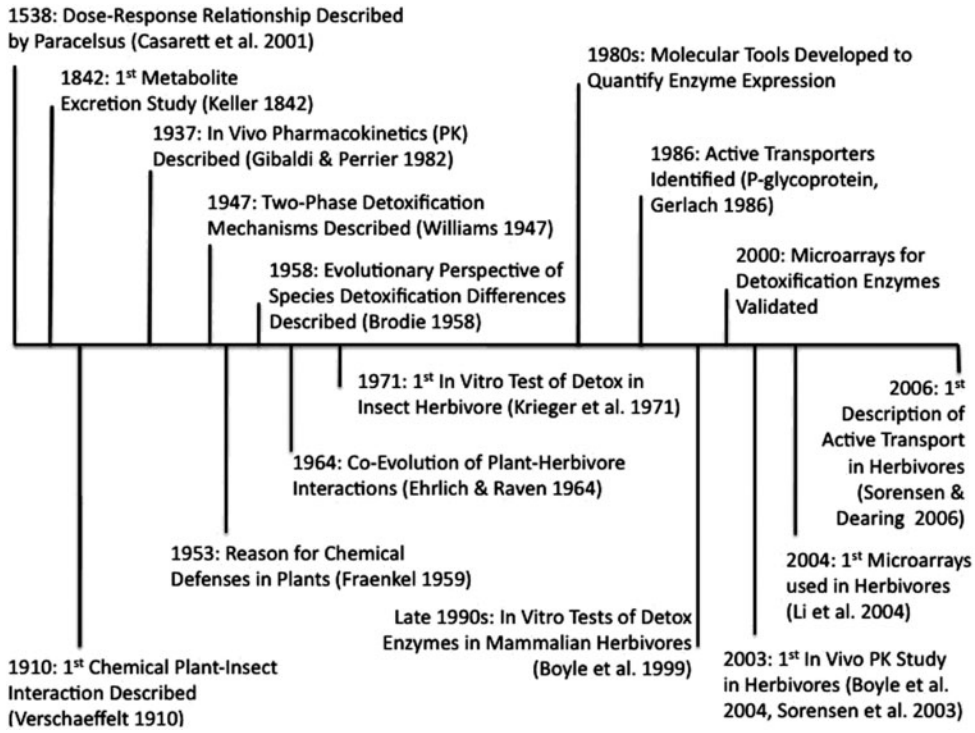

Fig. 1 A general time line (not to scale) of major research developments in pharmacology (top portion) and subsequent application of pharmacological approaches by ecologists studying plant–herbivore interactions (bottom portion).

herbivores in 1974. However, it was not until the late 1990s that pharmacological approaches were applied to non-insect herbivores.

Although the delay between emergence of new approaches and techniques and use by ecologists is narrowing, ecologists are still not keeping up with pharmacological progress. For example, only a single study has linked the dose of SM (i.e., intake) with blood concentrations (i.e., pharmacokinetics) and behavioral response (i.e., pharmacodynamics) (Mclean et al. 2007). There is still little known regarding the mechanism of action (e.g., target receptor binding) of ingested SMs in consumers. In addition, understanding the mechanisms of SM absorption (Sorensen et al. 2004; Sorensen and Dearing 2006) and distribution in consumers has lagged significantly behind understanding metabolism and excretion of SM (Boyle et al. 2000; Lamb et al. 2001; Pass et al. 2002; Haley et al. 2008; Dearing et al. 2006). The application of pharmacogenomics in plant–herbivore interactions is in its infancy despite its potential to reveal the genetic variability that influences the co-evolution of plant–herbivore interactions (Li et al. 2004; Henery et al. 2007; Skopec et al. 2007). Finally, even the most routine pharmacological approaches in ecology are only now being utilized in some prey–consumer systems, like marine herbivores (Sotka and Whalen 2008) and most are still completely absent from studies in freshwater herbivores, herbivorous lizards, and frugivores.

Symposium articles

The PharmEcology Symposium aimed to improve communication and transfer of knowledge between pharmacologists and ecologists in an effort to shorten the delay between pharmacological advances and application of these advances by ecologists. In addition, the symposium served to formalize several testable hypotheses at the interface of chemistry, pharmacology, and the physiological ecology of consumers and identify the most appropriate assays, technologies, laboratories, and study systems to test these hypotheses. As a result, several reviews emerged that reveal the current status of many fields that can benefit from PharmEcology.

It has long been recognized that some species tolerate SMs in their diet better than others. Part of this is related to the dietary niche of the animal and, in particular, whether the animal specializes on a limited set of plants or eats more broadly. Shipley et al. (this issue) examine the evidence for the specialist and generalist dichotomy and refine predictions about the causes and consequences of narrow and broad diets in mammalian herbviores.

They reveal that the existing criteria for defining mammalian herbivores as specialists has remained ambiguous and inconsistent. In response, they propose a general ''specialization key'' that will help researchers place their subjects along a specialist–generalist continuum. Their effort to untangle the complexity of existing terms and definitions provides researchers with a common language that will facilitate pharmacological comparisons among different studies by different researchers.

Sotka et al. (this issue) provide a review of existing applications of pharmacological principles to interactions between aquatic species and their food plants. They emphasize the need for investigators to consider diverse taxa because there is an even greater potential in aquatic species for differences in the routes of intake and excretion (e.g., skin, gills, food). There exist startling differences in the tolerance of different marine herbivores to some SMs but no general understanding of how this has evolved. Sotka et al. argue that PharmEcology can provide insights into these broad evolutionary patterns. In addition, they note the likelihood of significant climatic and anthropogenic driven changes that may impact these interactions.

Forbey et al. (this issue) provide a novel perspective in interpreting the chemical explanations of dietary selection by herbivores. Ecologists largely still regard SMs as invariably undesirable components of the diet that should be avoided by animals when possible. However, this runs counter to the large body of literature in human and domestic animal nutrition about the benefits to health of many SMs. Furthermore, Forbey et al. highlight the differences between the way that plant SMs are regarded as ''punishments'' by ecologists, but are often seen as providing ''reward'' in studies of human addiction (Sullivan et al. 2008). Ecologists should consider the possibilities of animals exploiting biological activity of SMs as a ''self-medication'' behavior in an effort to mitigate factors that challenge homeostasis. Moreover, Forbey et al. propose that the probability of self-medicatory behavior occurring is dependent on both the cost of the homeostatic challenge and the potential toxicity of the SM. A homeostatic perspective provides a novel way of thinking about SMs that goes beyond traditional explanations of dietary selection.

Of course nutrients and secondary metabolites do not occur in neat, separate packages and animals must regulate their intake of both parts of their diets. Raubenheimer and Simpson (this issue) argue that the distinction between toxins, medicines and nutrients is often small and inconsistent. Consequently, they argue that ecology should adopt a more integrated approach, such as the geometric framework, to explore interactions more holistically. The geometric approach is now being applied to foraging in wild mammals (Felton et al. 2009) and provides a clear pathway for understanding tradeoffs and consequences of regulating the simultaneous intake of multiple nutrients and SM.

Where we go from here?

It is clear that PharmEcology draws on many existing disciplines but ecologists do not necessarily need to become experts in pharmacology to engage the concepts described here. Instead, ecologists should gain a general understanding of pharmacology from the literature (McLean and Duncan 2006; Sorensen et al. 2006) and foster collaborations and communication with pharmacologists. There are several areas of plant–herbivore interactions that would greatly benefit from a continued effort to integrate pharmacology and ecology.

Mechanism of action

It is still somewhat surprising that the cellular and molecular targets of SMs and the means by which these effects are transduced into changes in feeding behaviour are so poorly known. Most of the effort has focused on intake rather than on toxicological (e.g., punishment) or pharmacological (i.e., reward) outcomes. For example, Marsh et al. (2006) showed that common brushtail possums could mix their diets to achieve higher intakes only when the SM in that food were excreted via different metabolic pathways. An extensive series of studies have examined the metabolism and excretion of 1,8-cineole, a monoterpene that is consumed in large concentrations by folivorous marsupials, but monoterpenes appear to act as general CNS depressants rather than acting upon particular receptor targets (Boyle and McLean 2004; Boyle et al. 2005; McLean et al. 2007).

Presumably animals can monitor these upsets and adjust feeding accordingly. However, we know of only two studies that have implicated specific receptors in monitoring the effects of ingesting the SM of plants. Aldrich et al. (1993) dosed sheep with metoclopramide (a nonspecific dopamine receptor antagonist) and found that their intake of endophyte-infected tall fescue was increased and Lawler et al. (1998) found that ondansetron (a specific serotonin $5HT_3$ receptor antagonist) led to greater intakes of the *Eucalyptus* SM jensenone (a formylated phloroglucinol compound) in marsupial possums.

Since these drugs (metoclopramide and ondansetron) are widely used to reduce nausea and vomiting, both studies were interpreted as evidence that nausea was a general mechanism by which animals could detect and regulate their intake of SM of plants. *In vivo* studies such as these are valuable because they can measure effects in the whole animal but it remains possible that these drugs affect other processes such as gut motility (Torregrossa and Dearing 2009). However, the integration of *in vitro* studies that can identity molecular targets and can screen SMs as ligands are needed to complement advances in *in vivo* assays.

Taking it back into the field

Understanding the ADME of SMs can reveal the mechanisms whereby animals avoid becoming poisoned and the degree to which foraging might be constrained by the speed at which SMs can be biotransformed and excreted. The next challenge is to understand how these constraints influence free-living animals and how populations might vary in their capacity to deal with SMs. Doing so is not easy because ecologists still struggle to estimate the amount and quality of food eaten by wild herbivores. However, newer molecular approaches can provide links between variation in phenotypic traits and specific elements of the genome. These types of approaches (association mapping) are advanced in humans and domesticated plants and animals and will be facilitated by the identification of a broader array of candidate genes from both genome and transcriptome sequencing projects. Nonetheless, there are very significant challenges in doing so, even in human medicine (Nebert et al. 2008), and the application of genome-wide approaches is probably beyond the capacity of most laboratories working with wild species at this time.

Notwithstanding the greater availability of molecular data, a major problem in implementing these approaches is in measuring phenotypes of ADME in animals. In human studies, dosing with defined drugs and obtaining serial blood samples from which to derive kinetic parameters requires significant organization and resources. For animals (even domestic species), the challenges are greater. However, if we are to implement approaches, such as association mapping, to explain variation amongst populations, then we need to be able to rapidly phenotype many animals without seriously compromising the physiology that has developed in response to their specific dietary history. Dearing et al. (2006) outlined a sleeping-time assay that is applicable to assessing the capacity of one enzyme system. However, ecologists need to engage with pharmacologists to extend and refine pharmacological methods in the field.

Conclusions

The few pioneering ecologists that have ventured into the extensive pharmacological literature have discovered a wealth of technologies, assays, approaches, and direction to better define the evolutionary, ecological, physiological, and biochemical interactions between plants and herbivores. Discussions across disciplinary boundaries are required to continue to synthesize what ecologists have gained from pharmacology and define new directions and opportunities that exist. The PharmEcology symposium initiated this communication, resulting in a collection of reviews that will hopefully inspire ecologists in the field of plant–herbivores interactions to:

(1) Define breadth of diet more consistently so as to facilitate comparisons of pharmacological attributes of consumers among species and researchers (Shipley et al. this issue).

(2) Test vexing issues related to aquatic prey–consumer chemical interactions using pharmacological approaches (Sotka et al. this issue).

(3) Apply pharmacological principles to understand self-medication in animals as a foraging behavior that maintains homeostasis (Forbey et al. this issue).

(4) Investigate the interactions of SMs and nutrients with the nutritional and physiological ecology of herbivores (Raubenheimer and Simpson this issue).

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