



Inducible chemical defences in animals

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Phenotypic plasticity is extremely widespread in the behaviour, morphology and life-history of animals. However, inducible changes in the production of defensive chemicals are described mostly in plants and surprisingly little is known about similar plasticity in chemical defences of animals. Inducible chemical defences may be common in animals because many are known to produce toxins, the synthesis of toxins is likely to be costly, and there are a few known cases of animals adjusting their toxin production to changes in environmental conditions. We outline what is known about the occurrence of inducible chemical defences in animals and argue that there is immense potential for progress in this field. Possible directions include surveying diverse taxa to explore how general its occurrence may be and testing for selection acting on inducible chemical defences. Data on inducible chemical defences would provide insight into life-history tradeoffs by enabling novel tests of how time-costs and resource-costs affect life-history. If the synthesis of toxic compounds by animals proves accessible to manipulation, as it is in plants and fungi, this will open the way to refined estimates of the fitness costs of defence, ultimately providing a clearer picture of how plasticity evolves and is maintained in nature.

Synthesis

Inducible changes in the behaviour, morphology, and life-history of animals are extremely widespread, but surprisingly little is known about similar changes in the production of defensive chemicals. We outline what is known about the occurrence of inducible chemical defences in animals and argue that there is immense potential for progress in this field. Possible directions include surveying diverse taxa to explore how general its occurrence may be and testing for selection acting on inducible chemical defences. Data on inducible chemical defences would provide insight into life-history tradeoffs by enabling novel tests of how time-costs and resource-costs affect life-history. If the synthesis of toxic compounds by animals proves accessible to manipulation, we will be able to estimate the fitness costs of defence more precisely, and ultimately provide a clearer picture of how plasticity evolves and is maintained in nature.

Individual organisms often adjust their phenotype in response to environmental stimuli, a process known as phenotypic plasticity. Natural selection favours the evolution of plasticity if the induced phenotype is costly to produce but enhances fitness in some (but not all) environments (Via and Lande 1985, Van Tienderen 1991, Scheiner 1993, DeWitt et al. 1998, Sultan and Spencer 2002, Urban 2007). Plasticity has been a focus of research for decades due to its obvious contribution to morphological and behavioural diversity. Plasticity is also important for the development and maintenance of ecological patterns and processes (Miner et al. 2005), and it may contribute to speciation (West-Eberhard 1989, 2003, Pfennig et al. 2010).

Plasticity induced by natural enemies – such as parasites, predators, or competitors – can help defend individuals and increase survival. This form of plasticity is termed an inducible defence (Harvell 1990). Research on animals has identified inducible defences principally in behaviour,

morphology, and life-history (Harvell 1990, Tollrian and Harvell 1999), but adaptive plasticity could also occur in chemical defences, a type of inducible physiological response to enemies. One reason to expect the presence of inducible chemical defences in animals is that constitutive chemical defences are so widespread. Many animals are known to synthesize and store toxic secondary metabolites that defend effectively against predators and parasites (Toledo and Jared 1995, Schmid-Hempel 2005, Kicklighter 2012). These chemicals are termed constitutive in the sense that they are (supposedly) always produced, regardless of the presence or proximity of their target. Many animals therefore possess the genetic and physiological capability to produce defensive toxins. Moreover, the synthesis of toxins requires the maintenance and operation of specialized biochemical machinery and is presumably costly. Consequently, important conditions for the evolution of plasticity, including fitness benefits of chemical defence in the presence of

enemies and costs in the absence of enemies, may often be met (Harvell 1990, Tollrian and Harvell 1999). According to this hypothesis, induced chemical defences evolved by increasing the environmental sensitivity of ancestral constitutive defences. This idea is implicit in models of the evolution of phenotypic plasticity (Karbon and Baldwin 1997, p. 221). Available evidence is limited, but macro-evolutionary transitions in both directions between constitutive and induced defences have been observed (Thaler and Karban 1997, Heil et al. 2004, Campbell and Kessler 2013). In sum, it seems likely that inducible changes in the production of chemical defences are widespread in animals and may be just as important as other types of plasticity.

Inducible chemical defences may have been overlooked in animals because behavioral and morphological responses to enemies are so important and conspicuous that they have, in effect, distracted us from noticing more subtle changes in physiology or chemical composition occurring at the same time. Methodological difficulties associated with the analysis of minute samples of unknown chemicals represent an additional hurdle, but this has been alleviated by the availability of HPLC-DAD-ESI-MS (Hayes et al. 2009, Hagman et al. 2009). Recent technological advances enabling fast and efficient separation (e.g. ultra-HPLC, monolithic or core-shell technology column) and allowing for accurate and sensitive mass-selective detection (e.g. high resolution MS, quadrupole time-of-flight tandem MS) further facilitate the identification of new components in small tissue samples.

This essay highlights recent discoveries of inducible chemical defences in three general contexts in which they could be important in the animal kingdom and describes the opportunities and benefits of future work on chemical response to predators.

Chemical defences induced by parasites and pathogens

Induced defence against parasites and pathogens is perhaps the most intensely studied area within the field of phenotypic plasticity due to its immediate relevance for human (and non-human) medicine. In vertebrates, the adaptive immune system responds to pathogens in a plastic and inducible manner, enabling hosts to recognize and quickly counteract diseases and parasite infections (Frost 1999). Outside the adaptive immune system, though, little is known about induced chemical defence against parasites. Such mechanisms are usually mentioned as part of the innate immune system in previous studies (Rollins-Smith 2001, Zasloff 2002). Many animal species, including vertebrates, employ non-specific chemical defences that can act as broad-spectrum antibiotics. These can exhibit activity towards bacteria, fungi, viruses, and are effective even against multidrug-resistant strains of pathogens (Nicolas and Mor 1995, Rinaldi 2002, Zasloff 2002, Rollins-Smith et al. 2005, Schmid-Hempel 2005, Mydlarz and Harvell 2007, Mangoni et al. 2008). We know of only two studies that have tested for plasticity in such non-specific chemical defences as a response to pathogens in vertebrates. Miele et al. (1998) discovered that adult *Bombina orientalis* toads increase the production of skin peptides after experimental exposure to

the bacterium *Aeromonas hydrophila*. Conversely, Mangoni et al. (2001) observed a sharp decrease in peptide synthesis in *Rana esculenta* frogs kept in sterile water as compared to control animals in naturally bacterium-rich water. With so few examples in vertebrates, it is far from clear how widespread pathogen-inducible chemical defences will prove to be.

Chemical defences induced by predators

Predators represent the second context in which inducible chemical defences may be important. Here again, there is abundant evidence of constitutive expression of toxic or unpalatable chemicals in a variety of vertebrates and invertebrates, and these very often serve as effective deterrents of predation (Toledo and Jared 1995, Kicklighter 2012). Furthermore, toxin levels can vary between life stages and among populations, and this has been interpreted as an adaptation to predictable temporal and spatial differences in predation risk and to the presumably high costs of toxin production (Kubaneck et al. 2002, Fordyce et al. 2006, Hayes et al. 2009). Predator-induced changes in toxin production are well-known in planktonic taxa and a few benthic invertebrates (Pohnert 2004). For example, Slattery et al. (2001) observed changes in the production of defensive metabolites in soft corals (*Simularia* sp.) after transplantation among sites exhibiting different levels of predation. Thornton and Kerr (2002) demonstrated that a cnidarian (*Pseudopterogorgia elisabethae*) produced more pseudopterogins, which may act as predator-deterrents, when attacked by a mollusc predator. Curiously, pseudopterogin production remained unchanged when animals were wounded artificially or preyed upon by a fish (Thornton and Kerr 2002). We know of only two reports of induced toxin production in vertebrates in response to predators. Toad metamorphs (*Anaxyrus boreas* and *Rhinella marina*) that had been raised with predators during the larval stage produced more toxins than their predator-naive conspecifics (Benard and Fordyce 2003, Hagman et al. 2009), illustrating that synthesis or storage of defensive chemicals can be environmentally-induced in vertebrates. However, these studies leave open the question of adaptive significance of induced antipredator responses in chemical defences because the risks of predation in the aquatic and terrestrial stages are not necessarily related.

Chemical defences induced by competitors

One mechanism of indirect interference competition involves chemicals produced and released by individuals that suppress growth or survival of competitors. This phenomenon – called allelopathy (Rice 1974, Reigosa et al. 2006) – has been demonstrated to play an important role in interactions among sponges, cnidarians, bryozoans and ascidians (Jackson and Buss 1975, Thacker et al. 1998, Engel and Pawlik 2000, Kubaneck et al. 2002, Pawlik et al. 2007, Chaves-Fonnegra et al. 2008). In these organisms, at least some of the compounds responsible for the allelopathic activity may be produced by surface-associated microbes (Lam 2006). Allelopathy is also described in freshwater zooplankton (Folt and Goldman 1981, Burns 2000). Interference competition among larvae of anuran amphibians has long been termed ‘chemical interference’ (Petranka 1989), although it is a unicellular alga (*Prototheca*) that suppresses the growth

of competitors: the proliferation of *Prototheca* in the intestines of tadpoles increases dramatically with the density of competing individuals and the scarcity of food resources, so the effect is one of competition-induced growth suppression (Griffiths et al. 1993). However, a recent study reported that the exposure to large toad tadpoles (*Rhinella marina*) during early, non-feeding developmental stages lowered survival and body mass of younger conspecifics (Crossland and Shine 2012), suggesting that allelochemicals may indeed play a role in interference competition among anuran larvae. Nonetheless, it remains unknown whether production of allelochemicals is generally induced by the appearance of competitors.

Outlook

A huge diversity of invertebrates, but also many fishes and amphibians that contain defensive toxins, could serve as model organisms for studies of inducible chemical defences. For example, anuran amphibians are known for depositing their eggs in a wide variety of water bodies, exposing larvae to unpredictably varying abundances of predators, competitors, and pathogens. This then creates conditions ideal for the evolution of phenotypic plasticity (West-Eberhard 1989, Harvell 1990). Species that show relatively weak inducible responses in behaviour or morphology, such as bufonid toads (Laurila et al. 1998, Lardner 2000, Van Buskirk 2002), may instead be relying on defensive skin secretions when facing parasites, predators or competitors (Toledo and Jared 1995, Wells 2007) and may be especially promising model organisms in studies of inducible chemical defences.

Studies on inducible chemical defences will expand our understanding of how animals respond to their environment. It is important to involve more animal taxa in studies testing for inducible chemical defence to determine how general its occurrence may be. To verify the presence of adaptive inducible chemical defences, we need experiments testing whether individuals facultatively adjust their toxin production to their environment, and whether induced changes enhance the fitness of individuals despite costs related to production or storage of toxins.

Data on inducible chemical defences will refine our understanding of life-history tradeoffs and the evolution of plasticity. Theory suggests that behavioural and morphological modes of response to enemies can have distinct fitness consequences, or may interact synergistically in their effects on fitness (Steiner and Pfeiffer 2007, Cressler et al. 2010, Higginson and Ruxton 2010). The two modes are involved in different kinds of tradeoffs, involving constraints in either time or resource acquisition, and probably function at different stages of the predation sequence. Chemical defence may prove to be similar to morphology, because it is costly to express and is therefore involved in a resource acquisition tradeoff. If so, inducible chemical defences will provide opportunities for testing predictions about how time-costs and resource-costs affect life-history transitions and overall investment in defence (Steiner and Pfeiffer 2007, Higginson and Ruxton 2010).

A sharper understanding of inducible chemical defences could also help establish a platform for performing more mechanistic experiments on the evolution of plasticity. In common with all types of inducible defence, the response

begins with perception of environmental cues reflecting the risk of encountering enemies (Harvell 1990). Subsequent steps, involving synthesis of the toxic compounds, may prove accessible to biochemical analysis and manipulation. In plants and fungi, the enzymes in question and their production pathways are currently the objects of intense study (Tag et al. 2001, Mao et al. 2011, Ahuja et al. 2012). Knowledge of expression pathways has enabled direct experimental manipulation of chemical production, yielding refined estimates of the fitness costs of defence (Meldau et al. 2012, Yang et al. 2012). Studying the underlying mechanism of toxin production and its genetic basis in animal model systems has similar potential to reveal how genetic variation for plastic responses arises, to test competing hypotheses about the adaptive basis of plasticity and, thus, should lead to a clearer picture of how plasticity evolves and is maintained in nature (Windig et al. 2004). In addition, because studies of plasticity in chemical defences target biogenic and bioactive chemicals, results may provide new insights in medicine, pharmacology, physiology, and agriculture (Daly et al. 1999, Proft 2009, Ujváry 2010). Thus, research on inducible chemical defences could spark both basic and applied research.

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