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The evolution of self-medication behaviour in mammals

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Self-medication behaviour is the use of natural materials or chemical substances to manipulate behaviour or alter the body's response to parasites or pathogens. Self-medication can be preventive, performed before an individual becomes infected or diseased, and/or therapeutic, performed after an individual becomes infected or diseased. We summarized all available reports of self-medication in mammals and reconstructed its evolution. We found that reports of self-medication were restricted to eutherian mammals and evolved at least four times independently. Self-medication was most commonly reported in primates. Detailed analyses of primates suggest that self-medication is a life-history trait associated with body size, absolute brain size and longevity, but we found no support for the hypothesis that self-medication evolved to reduce the costs of social living. Large, longer-lived species might thus benefit uniquely from self-medication.

ADDITIONAL KEYWORDS: life history – longevity – self-medication – wildlife disease.

INTRODUCTION

Self-medication is the use of natural materials or chemical substances to reduce or eliminate deleterious symptoms of parasites or pathogens (Clayton & Wolfe, 1993). De Roode *et al.* (2013) identified two broad types of self-medication: preventive (prophylactic), performed before an individual becomes infected or diseased or therapeutic (treatment), performed after an individual becomes infected or diseased. There is a growing literature that documents the taxonomic diversity of self-medication behaviour (e.g. Gradé *et al.*, 2009), but we do not have a general understanding of the evolutionary correlates of self-medication. Life-history theory provides a logical context through which we can study the evolutionary drivers of self-medication.

Life-history theory focuses on the trade-offs made by animals between allocation of energy to growth and reproduction vs. defending themselves against predators and parasites, in addition to trade-offs between reproductive investments and longevity (Stearns, 2000). Animals that live longer and explore varied environments are more likely to be exposed to parasites and pathogens; additionally, a well-described cost of sociality is an increased disease risk (Altizer *et al.*, 2003). In general, we predict that species that are more exposed to diseases are more likely to self-medicate to compensate for increased exposure.

Our broad survey focuses on mammals, and additional analyses were performed on primates, the order of mammals with the most reports of self-medication. We tested the general hypothesis that self-medication is a life-history adaptation associated with increased longevity and the various traits associated with this life-history syndrome. We also asked whether self-medication evolved in species with life-history traits that might lead to increased exposure to pathogens and parasites (e.g. those with larger home ranges, those with omnivorous diets that eat a wider range of foods, or those that live in larger social groups that interact with more potentially infected conspecifics).

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MATERIAL AND METHODS

Systematic literature review

To summarize the self-medication literature systematically, we used the Web of Science and Google Scholar. We searched for papers up to 14 May 2018 that described cases of self-medication in animals, even if they did not specifically use the word 'self-medication'. We searched the following keywords: 'self-medication in animals'; 'self-medication' AND 'animals'; 'parasite' AND 'defense animals'; ('parasite' OR 'pathogen') AND 'defense' AND 'animals' AND 'behav*'; 'self anointing in animals', 'prophylaxis' AND 'animals'; 'combat pathogens AND animals'; 'fur-rubbing'; 'anting'; 'transgenerational self-medication in animals'; 'self and anointing' AND 'defense'. In addition, we searched the bibliographies of those papers reporting self-medication for additional studies, especially some of the major reviews of self-medication (e.g. Newton, 1991; Huffman, 1997; Jain *et al.*, 2008; Lynch-Alfaro *et al.*, 2012; De Roode *et al.*, 2013). Finally, we also examined papers that cited relevant papers and reviews.

We found different levels of evidence in reports of self-medication behaviour; therefore, we classified reports as conclusive or inconclusive (Supporting Information, Table S1). Conclusive studies were those that demonstrated self-medication by quantifying: (1) the relationship between a specific self-medication behaviour and parasite or pathogen control or elimination; or (2) the relationship between the behaviour and a specific season with high incidence of the parasite/pathogen. We considered these reports as conclusive evidence of self-medication because they make a direct connection between the behaviour and the symptom or disease.

Inconclusive studies were those that suggested that the use of some plant or animal product was a form of self-medication without conclusively demonstrating it (e.g. Petit *et al.*, 2002). Inconclusive studies hypothesized the behaviour as self-medication through analogy either by suggesting that the same behaviour in other animals was an indication of self-medication, or by substance analogy, where the same substance was used by humans or other animals and thus could be considered medicinal. A few papers also described the deleterious effects of the substance used in the specific parasite/pathogen in the laboratory or the relationship between the behaviour and parasite load of the animal. All reports that did not have one of the two conditions used to define conclusive evidence were considered anecdotal/inconclusive.

By adopting two categories of self-medication, we aimed to reduce the effect of underestimating the occurrence of self-medication in animals. Additionally, we assumed that species not reported to engage in self-medication behaviour did not. Given the possibility of over attributing self-medication, we opted to perform two different sets of comparative analyses. We first treated species that had inconclusive evidence for self-medication as self-medicators. In our second set of analyses, we fully excluded species that did not have conclusive evidence for self-medication (i.e. species that inconclusively self-medicated were not included in the list of self-medicating or non-self-medicating species). In both the first and second approaches, we ran the same set of analyses but with a different species composition. Additionally, in both approaches, we weighted our confidence in reports of self-medication by adding a variable that quantified how intensively parasites and pathogens were studied for each species. Future studies will inevitably increase the number of conclusive reports of self-medication.

The evolution of self-medication in mammals

Assuming parsimony, and using Mesquite v.3.01 (Maddison & Maddison, 2014), we reconstructed the evolution of self-medication in mammals at the level of order and the evolution of self-medication in the order with most occurrences of the behaviour, Primates. We used the mammalian supertree of Bininda-Emonds *et al.* (2007) for our phylogenies.

Life-history correlates of self-medication in primates

We fitted phylogenetic logistic regressions (Ives & Garland, 2010) to identify relationships between self-medication and life-history traits in primates. Self-medication was binary (zero, no reports of self-medication; one, reports of self-medication), and the analyses followed the two approaches described above (i.e. treating inconclusively self-medicating species as self-medicators and excluding inconclusively self-medicating species altogether). Independent variables included brain size (Boddy *et al.*, 2012) and life-history traits obtained from the PanTHERIA database (Jones *et al.*, 2009). We might assume that we have more confidence in well-studied species compared with less well-studied ones. To control for this sampling bias, we used, for each species, the total number of publications listed in the Global Mammal Parasite Database v.2.0 as a measure of sampling effort. Then, we controlled traits by sampling effort and body size, adding these measures as independent variables in our analysis. Traits where there was no expectation that body size might be driving a correlation (e.g. diet breadth) were examined without including body size. For self-medicating species missing life-history information in PanTHERIA, where possible, we included life-history data from other sources (Supporting Information, Table S2). We analysed life-history traits in the program R v.3.5.0 (R Core Team & R Foundation for Statistical Computing, 2018) using the function phyloglm in the phylolm package (Ho & Ane, 2014). Missing values for life-history traits or species not included in the phylogeny cannot be handled in this framework. Thus, for each life-history trait analysis we included only species that had values for the life-history trait of interest and were included in the phylogeny. We identified 46 primate species that self-medicated (ten conclusive and 36 inconclusive reports), with 40 of the 46 species being listed both in the phylogeny and in the PanTHERIA database, and 22 of the 46 species with values of brain size from Boddy *et al.* (2012). There were 169 primate species considered non-self-medicating (i.e. where there was no evidence of self-medication) available in the PanTHERIA database and the phylogeny and 50 non-self-medicating primate species with values of brain size. Given that life-history data for any given trait (e.g. diet breadth) were not available for the full suite of 209 primate species and because species that had data for any given life-history (e.g. diet breadth) trait did not always overlap with species with other recorded traits (e.g. trophic level), we were limited to analysing each trait individually.

As a result, we fitted five phylogenetic multiple logistic regressions, respectively, for the following traits: body size ($\log_{10}$ mass in grams); absolute brain size ($\log_{10}$ mass in grams); diet breadth (number of foods eaten, ranging from one to eight classes: vertebrate, invertebrate, fruit, flowers/nectar/pollen, leaves/branches/bark, seeds, grass and roots/tubers); habitat breadth (number of habitat layers used by each species, ranging from one to four layers: above-ground dwelling, aquatic, fossorial and ground dwelling); and trophic level (omnivore or herbivore). Each aforementioned trait and sampling effort (N) were included as independent variables. We also fitted six phylogenetic multiple logistic regressions for the following traits, where each trait listed below, sampling effort (N) and body size ($\log_{10}$ body mass in grams) were included as independent variables: age at first birth ($\log_{10}$ days), home range size ($\log_{10}$ km^2), maximal longevity ($\log_{10}$ months), social group size ($\log_{10}$ individuals), population density ($\log_{10}$ individuals km^{-2}), and absolute brain size ($\log_{10}$ mass in grams). This resulted in a total of 11 models where we included species with inconclusive evidence of self-medication, and 11 models where we included only species with conclusive evidence. The total number of species included in each analysis ranged from 72 to 206 (including those with inconclusive evidence) and from 57 to 176 (including only those with conclusive evidence). The number of self-medicating species ranged from 22 to 40 (inconclusive) and from seven to ten (conclusive). Finally, the number of non-self-medicating species ranged from 50 to 166 in both approaches. The Supporting Information (Tables S1 and S2) contains all reports of self-medicating mammals along with the primate life-history traits used.

RESULTS

The evolution of self-medication

We found that a total of 71 different species from seven mammalian orders have been reported to self-medicate (Supporting Information, Table S1). Primates were the order with the most reports of self-medication (a total of 46 species with conclusive + inconclusive reports), followed by Carnivora (ten reports) and Rodentia (five reports). The majority of the remaining orders had only a few reports of self-medication. A parsimonious reconstruction of self-medication at the level of mammalian order suggests that it evolved independently at least four times, whether we include species with inconclusive evidence or not (Supporting Information, Fig. S1). In addition, a parsimonious reconstruction of self-medication in primate species suggests that it evolved at least 32 independent times if we include species with inconclusive evidence but only four times if we include only species with conclusive evidence (Supporting Information, Fig. S2).

Life-history correlates of self-medication in primates

The evolution of self-medication does not seem to be associated with increased pathogen exposure, as we initially hypothesized (Table 1; Supporting Information, Table S3). In both the analyses restricted only to conclusively self-medicating species, and in analyses including both conclusively and inconclusively self-medicating species, we found that species with larger bodies (inconclusive, $P = 0.008$; conclusive, $P = 0.049$) were more likely to self-medicate, as were species with larger values for absolute brain size (inconclusive, $P = 0.021$; conclusive, $P = 0.036$) and species with larger values for brain size controlled for body size (inconclusive, $P = 0.068$; conclusive, $P = 0.014$), with marginally significant results in the full data set. Also, species that live longer (controlled for body size; inconclusive, $P = 0.033$; conclusive, $P = 0.025$) were more likely to self-medicate in both approaches.

Using the full data set, habitat breadth ($P = 0.207$) and age at first birth (controlled for body size; $P = 0.413$) were not associated with self-medication, but presented marginally significant results in their association with self-medication in the more restrictive data set (habitat breadth, $P = 0.027$; age at first reproduction controlled by body size, $P = 0.029$).

Table 1. Results of additional simple logistic regressions including species with inconclusive evidence (1) and those with conclusive evidence (2) for life-history traits in primates

Variables	(1) Inconclusive evidence		(2) Conclusive evidence	
	Estimate	*P*-value	Estimate	*P*-value
Logistic regressions (+ sampling effort)				
Dietary breadth (number of classes)	0.02648	0.86808	0.08527	0.69867
Trophic level (omnivore/herbivore)	−0.58691	0.20020	0.00836	0.98521
Body size ($\log_{10}$ g)	1.31883	0.00836	1.74258	0.04964
Habitat breadth (number of layers)	0.55000	0.20733	1.42410	0.02702
Brain size ($\log_{10}$ g)	2.10432	0.02077	4.53306	0.03622
Logistic regressions (+ sampling effort; body size)				
Age at first birth ($\log_{10}$ days)	1.48193	0.41308	8.75406	0.02917
Home range ($\log_{10}$ km^2)	0.03583	0.91350	0.74755	0.17868
Maximal longevity ($\log_{10}$ months)	4.80238	0.03309	25.79795	0.02559
Social group size ($\log_{10}$ individuals)	0.15254	0.78357	−0.01619	0.98575
Population density ($\log_{10}$ individuals km^{-2})	−0.01063	0.97529	−0.03885	0.93484
Brain size ($\log_{10}$ g)	3.29265	0.06809	52.62264	0.01428

In contrast, diet breadth (inconclusive, $P = 0.868$; conclusive, $P = 0.698$), trophic level (inconclusive, $P = 0.200$; conclusive, $P = 0.985$), home range size (controlled for body size; inconclusive, $P = 0.913$; conclusive, $P = 0.178$), social group size (controlled for body size; inconclusive, $P = 0.783$; conclusive, $P = 0.985$) and population density (controlled for body size; inconclusive, $P = 0.975$; conclusive, $P = 0.934$) were not associated with the evolution of self-medication.

DISCUSSION

A variety of mammals engage in self-medication behaviour. Specific activities include the ingestion of whole leaves to expel parasites from the digestive system or soil to alleviate intestinal problems, done mostly by apes (Huffman *et al.*, 1997; Huffman & Hirata, 2004) and elephants (Houston *et al.*, 2001), fur-rubbing with citric acid plants to treat skin problems (Baker, 1996) and millipedes to avoid parasites (Zito *et al.*, 2003), as done by non-human primates, the placement of bay foliage around the nest to reduce the development of ectoparasites in dusky-footed wood rats (Hemmes *et al.*, 2002), and the use of specific plant substances to attenuate negative effects of food ingestion by artiodactyls (Villalba *et al.*, 2006). Given this diversity, what can we infer from an admittedly spotty record of reports of self-medication?

Taken together, we suggest that self-medication behaviour might have evolved many times in mammals and, in primates, self-medication might be a life-history trait associated with longevity, absolute brain size and body mass. Limiting the strength of this conclusion is the likelihood/possibility that self-medication behaviours are underreported in the literature and that the range of taxa in which the behaviour occurs is significantly larger. It is also possible that animals with pathologies self-medicate by manipulating their microbiome (e.g. by modifying food preferences), and this form of self-medication might not have been captured entirely by our methodology. Indeed, our lack of certainty precludes us from making strong statements about the exact number of evolutionary gains and losses of self-medication. Regardless, future studies will undoubtedly find more evidence of self-medication, but until then, our understanding is based on available data.

Self-medication might have evolved many times because of the availability or variability of natural products that can combat specific diseases. Alternatively, it might be costly to self-medicate mistakenly when it is not needed. For example, the consumption of a self-medicating substance can lead to toxic/anti-nutritional effects (Villalba *et al.*, 2017) and affect an individual's survival (Singer *et al.*, 2009). In that scenario, we would expect the costs of self-medication to be responsible for repeated evolutionary losses of self-medication.

Our results are inconsistent with the hypothesis that animals self-medicate to compensate for increased exposure to parasites and pathogens. Prior work has shown that animals that live in larger groups have more parasites (e.g. Altizer *et al.*, 2003; Arneberg *et al.*, 1998) and that there is a suite of compensatory behaviours (including self-grooming, allogrooming and grouping) to create a dilution effect to reduce infection (Mooring & Hart, 1992; Sánchez-Villagra *et al.*, 1998; Bordes *et al.*, 2007). Although we expected that self-medication might be added to this list, we found only weak support that it was a compensatory trait. Thus, although self-medication may profitably be viewed as an adaptation associated with increased longevity, the present data do not permit us to identify precisely how this occurs.

Although our comparative results explain differences between species in the presence or absence of self-medication, it would be extremely interesting to see whether such traits also vary intraspecifically. Are individuals that are exposed to more parasites and pathogens more likely to engage in self-medication? If so, do they engage in more self-medication? Future inter- and intraspecific data are required to evaluate these questions properly and, more generally, to gain a better understanding of how life-history variation drives both exposure to disease and behaviours to compensate for increased exposure. There is much to be learned about the evolution and maintenance of self-medication in mammals.

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AUTHOR CONTRIBUTIONS

Conceived the idea and directed the work: D.T.B. and B.N.-H. Collected the comparative data: A.B., L.C.N., E.S.A. and D.T.B. Analysed the data: E.S.A., L.C.N. and D.T.B. Wrote the first draft of the manuscript: L.C.N., E.S.A. and D.T.B. Edited the paper: all co-authors.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Reports of self-medication in mammals.
Table S2. Database of self-medication in primates used in analysis.
Table S3. Results of additional simple logistic regressions, including species with inconclusive evidence (1) and only those with conclusive evidence (2) for life-history traits in primates.
Figure S1. Parsimonious reconstruction of the evolution of self-medication in mammalian orders, including species with inconclusive evidence and only those with conclusive evidence.
Figure S2. Parsimonious reconstruction of the evolution of self-medication in primate species, including species with inconclusive evidence and only those with conclusive evidence.