# The Selective Pressures That Led to the Rarity of Venomous Mammals

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## Abstract

Mammals are not typically thought of as being venomous, yet venom is present in four orders: Monotremata (platypuses and echidnas), Eulipotyphla (shrews and solenodons), Chiroptera (bats), and Primates. Of the monotremes, only the male platypus is venomous, and unlike the other three orders, it envenomates through a hindlimb spur. The other three orders have venoms carried in salivary or other oral secretions and deliver them by biting or licking. Some Eulipotyphlans possess grooved teeth for venom delivery, which helps venom evolution be traced across their phylogeny. In Chiroptera, venom is restricted to the vampire bats for use in feeding, and in primates only certain lorises are venomous. Given the distant relationships in species between the orders, and the variety of environments each lives in, it is highly unlikely venom evolved only once. Instead, it is far more likely that venom evolved multiple times, with each order having its own specific reason. The emergence and retention of venom in mammals have a variety of hypotheses which are discussed and debated below. A particularly interesting case is that of the slow loris, which may have evolved venom for Müllerian mimicry with the spectacled cobra, a venomous species of snake.

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# Introduction

Compared to other groups of animals, the proportion of venomous mammals to non-venomous mammals is relatively low. Perhaps the unique combination of traits that make up mammals renders venom production cost-prohibitive, or simply unnecessary to be an effective competitor. It is also largely unknown what has pressured extant mammals into evolving and retaining their venom, another interesting aspect of venomous mammals.

The definition of venom and being venomous are a topic of debate, although, for this paper, the description by Fry et al. (2009) will be referenced. Fry et al. (2009) states that venom must be a secretion, produced in a specialized tissue in one animal and delivered into a target through wound infliction. The venom must also be composed of compounds that disrupt normal bodily processes in the target. Fry et al.'s (2009) definition identifies four orders of venomous mammals. These four orders are Eulipotyphla, Monotremata, Chiroptera, and Primates (Ligabue-Braun et al. 2012). Most venomous mammals are within Eulipotyphla, consisting of shrews and solenodons. The other venomous mammals within each Order are the male platypus of the Order Monotremata, the vampire bats of the order Chiroptera, and the slow and pygmy lorises of the Order Primates (Ligabue-Braun et al. 2012). These species are not closely related and have different venom compositions, making a venomous common ancestor unlikely; it is far more likely to result from convergent evolution.

The usage of venom and its mechanism in mammals differ significantly between the groups. It is used for much more than defense, and can be delivered through a variety of apparatuses, such as teeth or spikes (Ligabue-Braun 2017). The definition of venom used above is important over more restrictive reports involving apparatuses, as these definitions do not include Orders Chiroptera and Primates. Venomous chiropterans feed using toxic saliva, and venomous primates have a gland that they lick and subsequently spread to their tooth comb. This process is typically used for intraspecific signalling (Ligabue-Braun et al. 2012).

The idea of venomous mammals is also quite a recent one in scientific literature. Literature concerning venomous mammals only started being written around 100 years ago, and much is still unknown. Platypus envenomation, for example, is extremely painful and long-lasting yet conventional painkillers do not provide any relief against the pain (Whittington et al. 2014). Venomous mammals are also much less of a threat to humans than other venomous animals, which has led to a lack of research on antivenoms and the properties of mammal venoms. The variety of purposes that mammal venom has, as well as its rarity amongst mammals, give it a huge possibility for a wide range of applications from healthcare to evolutionary history. The aim of this review is to discuss why venomous mammals are rare and what led the extant species to evolve their unique venoms.

# EULIPOTYPHLA

Most extant venomous mammals exist in the Order Eulipotyphla, with five known venomous species and 18 suspected ones (Kowalski et al. 2021). Although this Order contains the most venomous species of any mammalian Order, only five of more than 400 species are venomous. The rarity of extinct venomous Eulipotyphlans is unknown, but there are two main hypotheses on their status. Fox et al. (2005) used *Bisonalveus browni*, a small mammal in *Cimolestes* from the Paleocene, as an example of one of the first potentially venomous mammals. They state that this species has a large vertical groove on the anterior side of the upper canines which they postulate as a venom delivery system by comparing it to a boomslang, a snake which possesses a similar groove. They also discuss other Paleocene fossils with parallel grooves along their teeth, arguing that venomous mammals were more common in the past (Fox et al. 2005).

Similarities within mammalian teeth grooves are not the most probable theory, as grooved teeth alone are not enough to assume venomousness. Species that may be venomous must be phylogenetically placed between two or more extant species already known to be venomous (Follinsbee 2013). Furthermore, while grooves in teeth can be used for venom delivery, assuming that the presence of a groove definitively means venom is premature. Many non-venomous species of mammal, like baboons, also have grooved teeth, which are most likely used to increase tooth strength against bending pressures (Follinsbee 2013). It is an ill-informed assumption that the presence of grooves, as argued by Follinsbee (2007), present within certain species of Eulipotyphla, such as *Dolinasorex*, proves venomousness. *B. browni*, within the same Order, is venomous. However, the assumption that species relationships within the Order, the presence of venom, and any correlation with dentition are not likely, due to the rarity of the trait within the Order today. The second hypothesis, that venomous Eulipotyphlans have always been rare, is more plausible on the above basis that grooved teeth are often assumed to mean venomous when they usually do not. Follinsbee (2013) states that venom is a newer trait among Eulipotyphlans that independently evolved three times. If venomous was the Eulipotyphlan ancestral condition, it would have had to have been lost nine separate times as while solenodons split from the rest of the Order relatively early, the other species are more closely related (Follinsbee 2013).

There are several suspected reasons why extant Eulipotyphlans evolved their venoms. Kowalski et al. (2021) state that the three selective pressures for venom evolution are food acquisition, biotic interactions, and defence and protection. Eulipotyphlan venom is weak and does not cause immediate effects, so what is most likely is food acquisition. Solenodons and shrews are both primarily insectivores; however, the role of venom in food acquisition among venomous mammals is unknown. This is known as the hunting big or hoarding small debate. Cuenca-Bescós (2007) uses an extinct giant shrew from the early Pliocene, *Beremendia fissidens*, to argue that venom evolved for hunting larger prey. *B. fissidens* are seen as effective large-prey hunters due to their large body size, larger envenomation apparatus, and strong bite force. These hunting adaptations effectively render large prey unconscious for later consumption (Cuenca-Bescós 2007). Furió et al. (2010) instead argues that the bending of the coronoid processes of *B. fissidens* allows the posterior teeth to hold small prey, presumably a beetle or gastropod, while the molars continue to increase pressure on the prey, rendering it immobile. The prey would then be envenomated through the lower incisor, the venom apparatus, and rendered comatose for later consumption (Furió et al. 2010).

Eulipotyphlans, being small animals, have a very high basal metabolic rate (BMR). An increased BMR requires a consistent food supply, and Eulipotyphlan venom has a critical role in food hoarding. Since their BMR is so high, constantly having to wander in search of food would be dangerous as Eulipotyphlans would constantly be exposing themselves to predation. Both venomous and nonvenomous Eulipotyphlans store invertebrates and larger prey (Kowalski et al. 2018); however, venomous ones possess a more effective and quicker means of doing so. Martin (1981) demonstrated that *Blarina brevicauda* paralyzes insects with its venom and stores them in their den for three days. The venom allows the insects to remain alive and very nutritious, yet incapable of escape.

Kowalski et al. (2018) also observed that venomous shrews tended to eat smaller prey immediately but immobilized and stored larger prey for later. This behaviour of either immediate consumption or storage fits with Optimal Foraging Theory (OFT). OFT hypothesizes that predators choose higher energy prey and attempt to minimize foraging time (Kowalski et al. 2018). It is far more time and energy-efficient to take fewer trips back to the den with larger prey than several trips with smaller prey.

Another theory is that Eulipotyphlans evolved venom for digestive purposes. Lawrence (1945) proposed that since Eulipotyphlans consume large amounts of protein in their diets, proteolytic enzymes in their venomous saliva would help them digest their food. While unfortunately no studies have confirmed this in venomous Eulipotyphlans, it could be possible given their high BMR and diet.

There are a variety of hypotheses as to why extant venomous Eulipotyphlans are rare. Venom may be too costly to produce when less energetically expensive methods of predation exist, or only specific species can profit off venom production (Kowalski

2021). However, the most notable are the tooth-and-claw concept and the past over-predation concept.

The tooth-and-claw concept suggests that Eulipotyphlans do not need venom because they have teeth and claws to hunt. Venom, no matter how advanced, is never instantaneous whereas physical weapons like teeth and claws can be immediately effective (Kowalski 2021). Since shrews require a consistent food supply, and death by venom takes time, species may have lost this ability in order to compete effectively. Some species of shrews can only survive up to 5 hours without food (Taylor 1998). However, since venom was most likely not the ancestral condition of Eulipotyphla (Follinsbee 2013), perhaps lineages containing venomous Eulipotyphlans went extinct or lost their venom as their physical weapons evolved.

While venom in Eulipotyphlans does play an essential role in minimizing energy expenditure while reducing damage sustained (Dufton 1992), especially in larger prey, most Eulipotyphlans are not known to possess venom, yet are still successful predators. Perhaps the extant venomous species had exceptional evolutionary conditions that required venom to remain competitive. Perhaps extant venomous Eulipotyphlans will go extinct as their venom becomes too costly to maintain in the evolutionary arms race.

Another possibility is the concept of past over-predation. Past venomous Eulipotyphlans, like the solenodon, may have consumed significantly more vertebrate prey than their modern insectivorous counterparts (Dufton 1992). Modern Eulipotyphlans still hunt vertebrates, but primarily stick to insects. Their prey choice may be due to the extinction of their original prey source resulting from overhunting. Predators can only maintain a stable relationship with their prey if they cannot prey on animals larger than themselves (Dufton 1992). If this balance weighs in favour of the predator, the prey can go extinct, and the predator must find a new food source or go extinct themselves. Dufton (1992) proposes that through venom, ancient solenodons may have hunted their vertebrate prey to extinction and had to adapt to a new, more reliable food source like insects. The resulting shift to insectivory could have caused most Eulipotyphlans to lose their venom, as it was no longer needed to hunt insects (Kowalski 2021). Perhaps the extant venomous Eulipotyphlans retained their venom as their niche still contained enough vertebrates to warrant venom, or it provided some benefit for hunting insects.

Another possibility is that venomous Eulipotyphlans are not that rare at all. There are 452 species in Eulipotyphla, and the presence of oral venom in most is unknown (Follinsbee 2013). Venomous Eulipotyphlans may be far more common than currently known simply because of a lack of testing. This seems unlikely as if venomous mammals are rare in general, it does not make sense that a high proportion of Eulipotyphla would be venomous. Mammals already have several efficient evolutionary traits for predation that venom seems unneeded for most of them given their successes in its absence.

## MONOTREMATA

The Order Monotremata contain five species, of which only one, the male platypus (*Ornithorhynchus anatinus*), is venomous. Their venom delivery system is called the crural system with a spur on each hindlimb, both connected to a pair of modified sweat glands called crural venom glands (Whittington et al. 2014). *Ornithorhynchus* defensin-like peptides, or OvDLPs, which the venom-like beta-defensin, or DEFB-VL genes produce, make up platypus venom (Whittington et al. 2008). These genes were duplicated three times, with the last duplication occurring 47 million years ago before the platypus and echidna split off between 34 to 17 million years ago. This separation would imply that their last common ancestor was venomous (Whittington et al. 2008). The break also suggests that although the platypus ancestor may not have resembled the extant platypus, the ancestral line that developed into the platypus from 34 to 17 million years ago was always venomous.

The four species of echidna are not venomous, unlike their ancestor. While two species of echidna still retain the crural system with both the gland and the spur, the latter being lost in females at maturity, it is not active (Whittington et al. 2014). In echidnas, the spurs do not serve much of a purpose due to the absence of venom. However, they do still use their gland as a scent gland (Whittington et al. 2014). The echidna ancestor was aquatic (Phillips 2009), making scent glands energetically inefficient, but as the ancestor transitioned onto land, the evolution of a scent gland would serve a useful function. As they were evolving to use the gland as a scent gland, they were losing their venom, as unlike the platypus, echidnas have developed an effective physical defence mechanism. The echidna's spines alone may have been enough to fend off predators, making venom energetically unfavourable and causing it to regress (Whittington et al. 2014).

Since only male platypuses have venom, it is currently used for reproductive purposes like intraspecific competition. Male platypuses with spur marks and limb paralysis are known results of such competition (Temple-Smith 1973). While used for reproductive purposes today, it potentially evolved as a defence mechanism. This theory implies that being venomous might have been an ancestral trait for all mammals. However, venom becomes secondarily lost in both metatherians and eutherians (Hurum et al. 2006). The venomous spur of the platypus is composed of three parts: the *cornu calcaris* core, a keratinous sheath around the core, and the *os calcaris* which attaches to the muscle of the platypus and allows the spur to stiffen, which it then uses to attack (Whittington et al. 2014). The *os calcaris* exists within three ancient mammal groups from various parts of the Cretaceous period: the symmetrodontans, the multituberculates, and the eutriconodontans (Hurum et al. 2006).

While the three species of multituberculate with an *os calcaris* are notable, the symmetrodontan and eutriconodontan representatives have far more known of their structure. Both the symmetrodontan *Zhangheotherium quinquecuspidens* and the eutriconodontan *Gobicondon ostromi* from the early Cretaceous had the *os calcaris* and the *cornu calcaris* preserved, with *G. ostromi* having evidence of it being sexually dimorphic as well (Hurum et al. 2006). Within the *cornu calcaris*, however, lies the possibility that neither species were venomous. In monotremes, the spur is hollow; however, in *Z. quinquecuspidens* and *G. ostromi* the spur is solid. Whether the species listed above lost their venom or the ancestral mammalian condition was never venomous is unknown (Hurum et al. 2006). If venomousness were the ancestral condition it would have been helpful as mammals were small and preyed upon frequently by various dinosaur species.

This theory is possible, but unlikely. As mentioned with Eulipotyphla, it is a bold assumption to conclude that a species is venomous based on one particular feature. As Follinsbee (2013) notes, species should also be able to be placed between two or more known venomous species. Furthermore, just because an extant species, like the platypus, has a feature that an extinct ancestor has, it does not mean it has the same function. Hurum et al. (2006) addresses this by acknowledging that both *Z. quinquecuspidens* and *G. ostromi* have solid spurs, and without the groove for venom delivery that the platypus possesses, there is uncertainty about how the spur is useful for venom injection.

Since therians and monotremes split around 166 million years ago and two of the three gene duplications required for venom peptides in platypuses occurred after this event, it is unlikely that venom would be the ancestral mammalian condition. Instead, only the monotremes would have this ancestral condition (Whittington et al. 2008). Cretaceous mammals had other physical means of defence, so the potential of venom was not the only means of protection they possessed. They would have still been prey of dinosaurs (Hurum et al. 2006), but they would have had some way of defending themselves.

Why platypuses have retained their venom is still largely unknown, but answers may lie within the venom composition. Platypus venom contains a variety of peptides such as OvDLPs, split into OvDLP-A, B, and C, OvCNP, and OvNGF. Of these, only OvDLP-A has been found exclusively in the venom gland (Whittington et al. 2009). While these are all components of venom, this suggests that the venom has far more use within the platypus than just intraspecific competition. OvDLPs are evolutionarily related to beta-defensins, a group of peptides with antimicrobial properties (Whittington et al. 2008). These OvDLPs are useful in platypus young, as through their mother's milk they receive incomplete immune protection. The OvDLPs therefore are hypothesized to provide an antimicrobial function in platypus young (Whittington et al. 2014).

OvDLPs are also an essential component of the mature platypus immune system. In adult male platypuses, the beta-defensins do not protect the venom gland (Whittington et al. 2009). OvDLPs thus may function as protection against self-envenomation, as OvDLPs may produce the swelling effects of the venom, which would be undesirable in the platypus itself (Whittington et al. 2009). This function is also essential for the platypus to maintain its immune system. Since only OvDLP-A is present exclusively in the crural gland, female platypuses would still produce other OvDLPs, but they would not need the protection against self-envenomation. Although the exact function of OvDLPs is unknown, perhaps they do retain some antimicrobial properties into adulthood beneficial to both sexes, which is plausible considering their evolution from the beta-defensins (Whittington et al. 2008).

OvDLP-A is restricted to the crural gland because it is the product of the last of three gene duplication events from 47 million years ago, and Papenfuss et al. (2008) proposed that the OvDLPs became more specialized with each duplication. The antibacterial properties of OvDLP-A specifically would be useful in the crural spur as the gland is exposed to the environment, making it more prone to infection. Other peptides in the venom, such as OvNGF and OvCNP, or the Ornithorhynchus nerve growth factor and the Ornithorhynchus C-type natriuretic peptide, are both related to the effects of the venom. These can include swelling, hyperalgesia, and hypotension (Whittington et al. 2008). These effects would serve the intraspecific competition that the males participate in and would ensure the fittest males survived.

Venom evolution in monotremes has a long and complicated history. As the oldest extant mammal group, and one that evolved in a solitary environment necessary to survive into the modern-day (Finlayson 2019), their venom has no doubt been helpful as marsupials and eutherians have slowly outcompeted them. While it may have initially evolved as a defence mechanism, today it serves various purposes that help ensure its continued survival. Their venom, or in the echidna, the loss of venom, only makes their presence and role in the environment today more interesting due to their inclusion within an ancient order.

# CHIROPTERA

The Order Chiroptera has three venomous representatives, all from the subfamily Desmodontinae. They are the white-winged vampire bat (*Diaemus youngi*), the common vampire bat (*Desmodus rotundus*), and the hairy-legged vampire bat (*Diphylla ecaudata*) (Ligabue-Braun 2012). The venomous saliva within all three hematophagous bats is an anticoagulant that contains plasminogen activators which allow for longer feeding periods (Ligabue-Braun 2012). Since their venom typically does not kill their prey, they operate parasitically and may not be considered truly venomous by other definitions. However, using Fry et al.'s (2009) definition, they do qualify as venomous and will be considered as such.

The three species of vampire bats have different diets and tracing the genetic history of their venom can reveal why it venom evolved as a useful means for feeding. All three species possess plasminogen activators, which are composed of five domains. The critical domains are the $K_2$ and F domains as they both competitively bind fibrin and plasminogen activator inhibitor 1, or PAI-1, which inhibits fibrin (Tellgren-Roth et al. 2009). The $K_2$ domain is the primary site of PAI-1, and both *D. rotundus* and *D. youngi* have lost the $K_2$ domain, giving them significantly enhanced fibrin binding capabilities, which allows their saliva to be much more effective since mammalian genomes contain PAI-1. Avian genomes do not possess PAI-1 (Tellgren-Roth et al. 2009). Since *D. rotundus* feeds exclusively on mammals, it has reduced their sensitivity to PAI-1 even further, which *D. youngi* does not need as it feeds on both birds and mammals (Tellgren-Roth et al. 2009). *D. ecaudata* preys only on birds and has not lost any domains of its plasminogen activators.

There are several more components of vampire bat venom that may explain why it evolved as a valuable means for feeding. The components of *D. rotundus* venom evolved through positive selection, meaning the addition of venom was beneficial to the ancestor (Low et al. 2013). However, not every mutation within *D. rotundus* venom dramatically affected the venom. One class of mutations is the Pituitary Adenylate Cyclase-Activating Polypeptide, or PACAP, which happens to be hypermutable. Although the propeptide region of PACAP was very conserved, it likely ensures that the other domains are efficiently liberated and excised, allowing them to mutate rapidly in a positive selection environment (Low et al. 2013). One theory proposes that these mutations in PACAP that seem neutral to venom function and structure and are instead there to improve the fitness of the vampire bat (Low et al. 2013).

PACAP may also have a in focal mutagenesis. Since PACAP mutations are not particularly important for the structure or function of venom and exist on the molecular surface, they serve two roles (Low et al. 2013). Firstly, the mutations in PACAP help maintain the integrity of the venom so the other components do not mutate the venom into something either too toxic or too weak for the bat to use (Low et al. 2013). However, the quick mutations that PACAP undergoes are critical for variation in the venom of each bat. The molecular surface can vary over time, but still works to preserve structure and function, preventing prey from developing resistance to the venom components (Low et al. 2013). If prey could develop resistance quickly, venom would no longer ensure a constant food supply, and the bat would quickly starve.

The adipose tissue of bats varies widely depending on their diets and the time of year. Most bats maintain relatively low adipose levels to sustain flight and typically increase their adipose stores during the rainy season as food is more abundant (Freitas et al. 2006). Vampire bats are unique as they do not possess adipose stores, meaning they cannot rely on them for storage. Without this storage, vampire bats require a constant food supply, and can die of starvation in as little as two days (Ligabue-Braun 2017). The venom of vampire bats allows them to feed on their prey without disturbing them for up to 30 minutes. This allows them a much more consistent and sufficient food supply. Venom helps to counterbalance the loss of fatty tissue, as a solely insectivorous bat would not be able to survive without it. Since wild insects are more challenging to eat than domestic animals like cattle, whose populations sizes do not correlate with environmental conditions, this adaptation is advantageous.

Furthermore, vampire bats are poor thermoregulators (Freitas et al. 2006). Adipose tissue helps insulate and maintain the body and other bat species can rely on this to maintain their body temperature. Since vampire bats do not possess adipose tissue, they rely on the constant supply of blood, either through feeding or food sharing, to maintain their body temperature as it can cool down significantly during the nights of the dry season (Freitas et al. 2006). This poor thermoregulation, combined with the constant feeding requirement, can explain why the need for venom in bats is so rare. In most species, these requirements would be tough to maintain as without the venom for a consistent food supply; they would die very quickly.

Obligate sanguivory is very rare. Vampire bats are the only mammals that practice this form of predation. Baker et al. (2012) propose that vampire bats evolved from insectivores and gained their sangivorous traits to aid avian predation. Of the three species of vampire bats, *D. ecaudata* is the oldest and its genus is estimated to have split from the other vampire bats between 22.4 and 21 million years ago during the Miocene (Baker et al. 2012). Since *D. ecaudata* feeds exclusively on birds, it has minor adaptations in its venom, indicating that the vampire bat ancestor likely preyed on avifauna. Since birds are diurnal, the venom would have allowed for quiet, undisturbed nocturnal feeding by the vampire bats (Baker et al. 2012). Furthermore, since sanguivory was new to vampire bats they did not have as many of the adaptations as they do today, so they might have needed more substantial quantities of blood. This would be possible since large birds like pelicans have existed as early as the middle Eocene (Osborn 1910).

Perhaps venomous bats are so rare because their adaptations for this new niche were very sudden.

Sanguivory evolved between 26.11 and 21.67 million years ago, or over 4.44 million years (Baker et al. 2012). That time frame is tiny for such a significant lifestyle change. The number of adaptations the vampire bat would have acquired in that time frame, including venom, to facilitate sanguivory is incredible. No other bat species has undergone anything this significant so rapidly (Baker et al. 2012), so perhaps other bats never had a reason to evolve venom.

Another potential reason that venomous bats are rare is that sanguivory makes them highly vulnerable to disease. For bats in general and vampire bats specifically the most prevalent disease is rabies. Since the 1970s, rabies has spread to cover 100% of *D. rotundus*' range, and human and livestock cases have been increasing (Johnson et al. 2014). Vampire bats are dangerously effective at spreading rabies to their prey as the rabies virus is predominant in their saliva (Johnson et al. 2014). They are also highly effective at spreading rabies to other bats through antigenic variants, or AgV-3, which are normally associated with *D. rotundus* yet are found in 71.4% of other bat species sampled by Johnson et al. (2014). This very high and effective transmission rate shows that sanguivory poses a serious danger to vampire bats, mainly since lethal infections of rabies within vampire bats only occur around 10% of the time, allowing the virus to proliferate in populations (Johnson et al. 2014).

Vampire bats are highly specialized animals, especially being the only obligate sanguivorous mammals. They have unique evolutionary histories, physiologies, and genomic adaptations which allow them to maintain their venom while also keeping it rare amongst other Chiropterans. Their venom has made their sanguivory possible; without it, sanguivory would not be sustainable. It is also of interest that the use of venom has changed very little over time, since species like *D. ecaudata* still feed exclusively on birds (Tellgren-Roth et al. 2009). It seems that despite all the risks, venom remains a clear advantage for the three species of vampire bats.

## PRIMATES

There are four species of venomous lorises from the genus *Nycticebus*. They are *N. coucang*, *N bengalensis*, *N. kayan*, and *N. pygmaeus*, all which possess a brachial gland that secretes venom. The prosimian then licks the gland which activates the venom and spreads the mixture along their toothcomb or rubs it into their fur (Ligabue-Braun 2017). Although they are considered venomous using Fry et al.'s (2009) definition, they are unique compared to other venomous mammals. Prosimians are indirectly venomous since their venom delivery system has no relation to their brachial gland (Ligabue-Braun et al. 2012). Loris' venom may have connections to the ape ancestor as well. The primary toxic agent of loris venom is brachial gland exudate, or BGE. BGE proteins have been found in the human genome as pseudogenes, implying more primates could have been venomous in the past (Ligabue-Braun 2017).

One of the potential reasons for loris venom evolution is ectoparasite defence. Studies conducted on venomous lorises demonstrated extremely low levels of ectoparasite infection (Rode-Margono et al. 2015). The main ectoparasite for lorises are ticks, and loris venom may prevent tick infestations. When arachnids, including ticks, were exposed to the venom and saliva mixture, 78% died after one hour of exposure (Rode-Margono et al. 2015). This form of defence would be valuable for lorises, as primates often suffer from ticks and other ectoparasites. Primates often practice grooming to reduce parasites, but lorises have several behaviours, such as solitary torpor, that might necessitate different forms of ectoparasite management (Nekaris et al. 2013). There is also evidence that the compound protects against other ectoparasites like leeches, as when Nekaris et al. (2013) exposed 12 leeches to BGE and saliva, they died instantaneously.

Lorises may have evolved their venom in an interesting case of Müllerian mimicry. The slow loris possesses remarkably similar characteristics to the spectacled cobra, or *Naja naja* (Nekaris et al. 2013). Some species of venomous loris have patterning, defensive postures, and make hissing noises during aggression, all of which can be indistinguishable from those of a spectacled cobra (Nekaris et al. 2013). If Müllerian mimicry indeed is occurring, it would be beneficial for both venomous lorises and *N. naja* as olfactory predators would only need to attack one to know they are both venomous and not suitable prey. For Müllerian mimicry to occur, both mimics and the predators must have had overlapping ranges and some selective pressure must have been happening specific to the mimics (Nekaris et al. 2013).

Sometime in the past, both *N. naja* and *Nycticebus* must have coexisted. *N. naja* arrived in Asia ten million years ago, and lorises arrived eight million years ago (Nekaris et al. 2013). During this time, savannah ecosystems replaced the tropical rainforests of Southeast Asia, which would have been disadvantageous to lorises as they are primarily arboreal (Nekaris et al. 2013). Traversing the open ground would have been very dangerous to lorises and increased their risk of predation. In long grass, markings like those of a cobra could have been enough to prevent predation of the loris. These markings would have been selected for in lorises, as predators recognized the cobra as dangerous prey.

Venomous lorises may have maintained their venom for communication. Lorises communicate primarily through olfactory signals, often through urine, however venomous lorises can use their BGE (Hagey et al. 2007). Venomous lorises can either rub various parts of their body against the brachial gland or lick the gland and apply the BGE to their body, which other lorises can use to determine the age, health, dominance, etc. of the scented loris (Hagey et al. 2007). Since lorises can be very social, these olfactory signals are useful intraspecific communication tools. With all the information available to other lorises through scent, perhaps it has a use in competition and mating amongst male lorises.

Although other lorises compete using urine, BGE has some advantages over urine that might explain its retention. BGE is composed primarily of aldehydes, aromatics, and ketones which make it short-lived, but highly potent and powerful, all while containing a large quantity of information (Hagey et al. 2007). BGE acts as a molecular box. When BGE is in the gland on the arm, a hydrophobic environment, the box is open and species-specific signalling molecules can enter (Hagey et al. 2007). The loris then licks the gland, exposing BGE to water, the box closes, and BGE enters into the environment by the process of topical application (Hagey et al. 2007). Other lorises can then lick this compound, or it can remain in the environment. In both cases, the box will be removed from water and opened, allowing the information in the signalling molecules to be conveyed (Hagey et al.2007). This signalling method can be much more versatile than urine.

Intraspecific competition is another likely reason that loris venom is maintained. Venom may have originated as a warning signal against other lorises but evolved to become an actual venom (Nekaris et al. 2013). In both captivity and in the wild, lorises exhibit biting behaviour towards competition, often with severe consequences to both competitors. These can include necrosis, septicemia, and even death (Nekaris et al. 2013). The male lorises fight intensely for females and will lick their brachial glands and proceed to rub the secretion over their fur (Rode-Margono et al. 2015). A well-timed bite by a loris against a competitor would ensure that the attacking loris could mate with their desired female, especially is the competing loris is incapacitated.

Venom for intraspecific competition amongst lorises is an interesting reason to maintain venom, with the male platypus being the only other venomous mammal known to use its venom for this purpose. Competition is likely not the only factor leading to the retention of venom or the females would have lost the capability to produce venom, like the female platypus (Whittington et al. 2014). One disadvantage of using venom for intraspecific competition is that venom is metabolically expensive, so producing and deploying venom when necessary is advantageous for venomous lorises only for brief periods of time. It would be interesting to see if there are records of female lorises attacking other females.

Venom may be rare amongst primates and lorises due to the lack of necessity. Many loris species are primarily exudativorous, however they also occasionally eat small prey and shoots (Starr et al. 2013). This means that they do not require venom for prey capture, so many lorises may not have evolved it as they do not hunt large prey. Furthermore, as mentioned above lorises can also use their urine to deliver olfactory information, so venom is not a requirement for intraspecific communication (Hagey et al. 2007). Although venomous lorises are known to bite other lorises, often with severe effects (Ligabue-Braun et al. 2012), other non-venomous lorises still can compete. Lorises have grasping digits so they can fight with their teeth and claws.

Primates are intelligent, meaning they can overcome problems without the use of venom. Perhaps the intelligence of primates helped reduce their need for venom as they could deduce other solutions. They are known to have very complex and diverse social structures, so this group dynamic could help protect them from situations where venom is otherwise necessary for other species. According to Nekaris et al. (2013), mimicry is rare in mammals so the conditions leading to venomous lorises have not really been replicated across other mammals, leading to an overall lack of venom amongst primates. The prevailing idea is that primates as an order mostly do not need venom due to their anatomy and social structure, and overall, it would be energetically inefficient.

## CONCLUSION

This paper aimed to discover why venomous mammals are rare and why extant venomous mammals have retained their venom. Through looking at the four venomous mammal orders, those being Monotremata, Chiroptera, Eulipotyphla, and Primates, the above questions have successfully been answered. While there remain some unknowns, with the current research available everything possible was synthesized to get the most comprehensive answer.

Beginning with Eulipotyphla, the venomous shrews and solenodons probably evolved their venom to aid prey acquisition, which they still use it for today. In the past, Eulipotyphlans used their venom for hunting big or hoarding small (Furió et al. 2010) although they primarily use it now for smaller prey. They may be rare because they have teeth and claws that act faster than venom can. (Dufton 1992) also proposes that ancient solenodons were too successful at hunting their vertebrate prey, rendering the prey extinct and thus forcing them to switch to insectivory. This over-hunting also reduces the effectiveness of venom.

Continuing with Monotremata, they likely evolved their venom for defensive purposes (Hurum et al. 2006). Venom would have been useful in protection from predators as unlike echidnas, platypuses do not have spines. Venom is likely maintained as an anti-bacterial defence in altricial platypuses, as the protection in platypus milk is incomplete (Whittington et al. 2014). Venomous attributes are rare amongst monotremes because it is unnecessary, as echidnas have their spines and platypuses use their venom for intraspecific competition.

Chiropterans evolved obligate sanguivory over a tiny 4.44 million years (Baker et al. 2012), and their venom evolved to aid in their sanguivory. Without venom, sanguivory would not be sustainable. They most likely evolved to feed initially on birds (Baker et al. 2012) and transitioned to feeding on mammals. It may be rare amongst Chiropterans because it evolved so quickly that it has not yet had time to evolve in other bats. It also has many risks, such as exposure to blood-borne pathogens, that make it a potentially dangerous mode of feeding.

The last of the venomous mammals are the venomous lorises of the Order Primates. They potentially evolved their venom as part of an elaborate case of Müllerian mimicry. They have several behaviours and physical characteristics, along with their venom, that causes them to resemble the spectacled cobra (Nekaris et al. 2013). It may be rare because primates do not need it given their intelligence, social structures, and physical capabilities. Nowadays the venom acts primarily as a signalling tool.

Overall, there are numerous hypotheses to explain the rarity of venomous mammals. These hypotheses include that mammals do not need it, venom is too expensive to produce and use, and venom is only valuable for specific morphologies (Follinsbee 2013). Mammals have other advantages, such as teeth and claws, that enable most extant ones to survive very successfully without venom. In extant venomous mammals, their venom use is specialized and often combined with other traits. In the lorises and platypus, venom aids in intraspecific competition (Temple-Smith 1973). This technique in intraspecific competition alone is scarce amongst mammals, so it would suggest that venom often is not needed for competition. Most mammals can be successful in their needs, whether they be reproductive, energetic, etc., without venom. The fact that some species require venom for some of their needs is an interesting evolutionary situation that perhaps came through the unique evolutionary history of the species or is a relic of a bygone era that has adapted to other uses.

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