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Is the Adipostatic Signalling Function of Leptin Conserved in Seasonal Vertebrates? A Systematic Narrative Review

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Is the Adipostatic Signalling Function of Leptin Conserved in Seasonal Vertebrates? A Systematic Narrative Review

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Simple Summary

This study reviews whether leptin, a hormone known for helping regulate body fat levels, has the same role in different groups of animals, including mammals, birds, reptiles, and fish. The study focused on animals that reproduce seasonally, as this may affect how leptin works. A total of 49 studies were explored; most were about eutherian (placental) mammals. Only a few studies examined other animals like birds, reptiles, and fish, therefore, it was hard to draw firm conclusions about those groups. However, current evidence suggests that leptin does not help regulate body fat in birds or fish. Some results from reptiles and non-placental mammals were unclear, and more studies are needed. In the 40 studies on 25 placental mammal species, leptin's fat-regulating role was not always found, suggesting it may work differently depending on the species. This review highlights the need for further research to understand how leptin functions in different animals and whether its role in controlling body fat is unique to certain mammal groups. This information could help improve our understanding of animal biology and how hormones evolve to support different ways of living.

Abstract

Using a systematic approach, this review investigates whether the adipostatic signalling function of leptin is conserved across the vertebrate taxa (mammals, birds, reptiles and fish), with a focus on seasonally reproducing species. Of the 49 studies analysed, only nine investigated sub-eutherian mammals (monotreme, n = 1; marsupials, n = 0 birds, n = 4; reptiles n = 2 and fish, n = 2); therefore, it was not possible to draw solid conclusions for these taxa. Nevertheless, the evidence collated in this review appears to suggest that an adipostatic function of leptin is absent in avian fish species. Further investigation is required for sub-eutherian and reptilian species as the presented results were inconclusive. Twenty-five species of eutherian mammals were investigated across 40 studies. The adipostatic signalling function of leptin was not observed in all eutherian species, leading to the suggestion of species-specific functionality which may extend to sub-eutherian mammals and reptiles. Further research is necessary across a variety of species of all taxa to confirm whether or not the adipostatic function of leptin is confined to therian mammals.

Keywords: leptin; adiposity; adipostat; seasonal vertebrate; systematic review

1. Introduction

Discovered in mice in 1994, the protein hormone, leptin, has been described as a satiety signal, synthesised and secreted by adipose tissue [1]. Leptin has since been identified in a wide range of vertebrate taxa including mammals, amphibians, fish, reptiles [2], and more recently, birds [3]. Further research conducted in eutherian mammals has shown leptin to have significant functional diversity with roles ranging from the regulation of reproduction and immune function to operating as an adipostat (regulating body fat within a narrow range based on energy intake and expenditure; [4]. This adipostatic function of leptin has been observed in a number of eutherian mammals, where

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an increase in adiposity is generally associated with increased circulating leptin concentrations [2]. Systemic leptin binds to receptors expressed in intracellular compartments of the hypothalamus (e.g., endoplasmic reticulum and endosomes)[5], regulating the production of anorexigenic neuropeptides. These anorexigenic neuropeptides reduce appetite and increase metabolic rate, resulting in a loss of adipose tissue; thus, regulating fat reserves [5].

While this adipostatic function would appear adaptive across species for keeping individuals in optimal body condition, many seasonally reproducing and seasonally hibernating eutherian mammals demonstrate circannual patterns of adiposity, purposely accumulating in large fat depots in preparation for periods of reproductive activity or hibernation [6,7]; clearly an adipostatic function of leptin in these species would be problematic. Consequently, many seasonally reproducing and hibernating eutherian mammals prevent loss of adiposity during these periods in one of two ways: (1) leptin resistance, where circulating leptin concentrations correlate with adiposity but hypothalamic receptors are resistant to the effects of elevated leptin concentrations [6]; or (2) leptin decoupling, whereby circulating leptin concentrations no longer correlate with adiposity [7].

As most studies have focussed on eutherian mammals, it is unclear if the adipostatic function of leptin is also conserved in sub-eutherian mammals or across the different vertebrate taxa. In the only study of the Monotremata [8] investigated the adipostatic function of leptin in the seasonally reproducing short-beaked echidna (*Tachyglossus aculeatus*) and reported a weak negative relationship between circulating leptin levels and body mass. While the short-beaked echidna lays eggs, they also possess a yolk sac placenta *in utero* for the transport of nutrients during the early stages of foetal development in a similar manner to viviparous therian mammals [9]. The echidna, therefore, represents an intermediate stage between oviparous reptiles and viviparous therian mammals. Given their unique biology, and noting a similar relationship between leptin and adiposity in a small selection of studies on reptiles [10], birds [11,12]; and fish [13], some authors speculated that the adipostatic function of leptin may be restricted to therian (Metatheria and Eutheria) mammals which separated from the Prototheria approximately 166 million years ago, or eutherian mammals which diverged from the metatherians approximately 148 million years ago [8].

In the 30 years since its discovery, there has been no review that has collated studies reporting the adipostatic function of leptin in mammalian and non-mammalian vertebrates. Using a systematic approach, this review will focus on seasonally reproducing and hibernating vertebrates from a range of taxa, including mammals, birds, reptiles and fish, in order to further investigate the hypothesis proposed by Sprent [8], that the adipostatic signalling function of leptin is confined to therian mammals.

2. Materials and Methods

The search engines used to identify papers were PubMed advanced search, using medical subject headings (MeSH) (1951– January 2021; and Web of Science, Core Collection, advanced search (1990–January 2019). Database specific search terms were created to ensure the database search contained literature relevant to the topic. The reference lists of included studies were also searched as an additional means of identifying appropriate studies. The inclusion criteria for studies identified in the searches were (1) peer-reviewed, (2) written in the English language, (3) empirically conducted research and (4) research which investigated the role of naturally circulating leptin levels in regulating adiposity in seasonally reproducing (where reproductive activity only occurs during certain times of the year) or seasonally hibernating (where species enter a state of inactivity and metabolic depression at certain times of the year), non-domesticated mammals, birds, reptiles or fish.

Titles and abstracts of all identified papers were examined against the pre-defined inclusion criteria. Where an article appeared to meet the inclusion criteria, the full text was obtained and then subjected to a second phase of screening to ensure compliance with the inclusion criteria. Each publication was then analysed for publication date, species data (e.g. Taxa, Order, species name (common and scientific), diet, gender, and whether the species is a long- or short-day breeder, captive or wild, mature or immature and whether or not the species engages in hibernation or migratory

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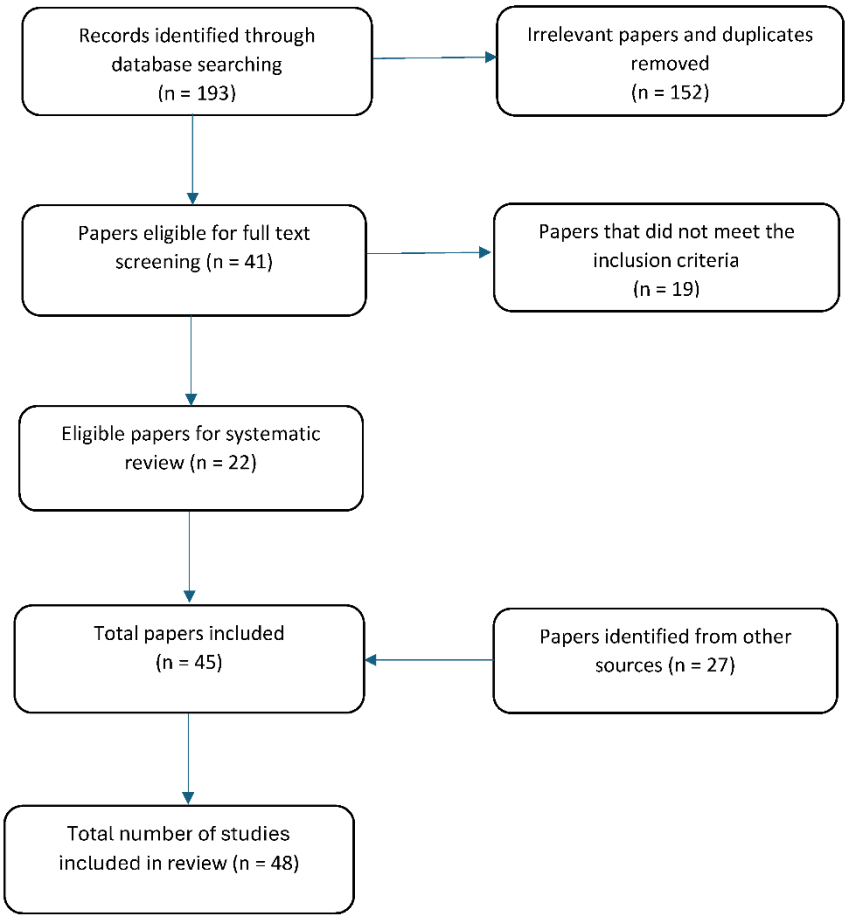
behaviour, number of animals included in the study, method of body fat determination and whether this method had been validated, duration of study and finally, a description of how leptin interacts with changes in adiposity in the species studied.

In order to determine if the function of leptin as an adipostat may be confined to specific groups of species, species were subsequently sorted into the appropriate categories including Order, diet, timing of seasonal breeding strategy (long-day or short-day) and whether the species hibernates or migrates.

3. Results

3.1. Database Search

A total of 193 publications were identified from electronic searching. Following the initial screening of titles and abstracts and after removal of duplicates, 41 publications were found to be eligible for full text screening, after which, 22 met the inclusion criteria. Discarded publications (n = 19) assessed exogenous leptin, were based on domesticated species, investigated other aspects of leptin, or the full publication was unable to be retrieved. An additional 27 publications were identified after cross-checking the references of those meeting the inclusion criteria, resulting in a total of 46 publications for review (Figure 1). These 46 publications referred to 48 separate studies as three publications investigated more than one species.



3.2. Leptin and Adiposity in Mammals, Birds, Reptiles and Fish

The identified studies represented all taxa of interest including 25 species of mammals (24 eutherians - placental mammals and 1 prototherian - monotreme mammal), four species of birds, two species of reptiles and two species of fish (Table 1); surprisingly there has yet to be any study that has investigated the relationship between adiposity and circulating leptin levels in metatherian mammals

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(i.e., Marsupials). Leptin was found to function as an adipostat in 18 species (72%) of eutherians; of these, six (33%) demonstrated leptin decoupling or leptin sensitivity during periods of hibernation or migration. In two separate studies conducted on the American mink (*Mustela vison*), Nieminen et al. (2000) reported that leptin did not function as an adipostat, whereas Tauson and Forsberg [14] suggested that it does. In the single prototherian species, the short-beaked echidna [8], and in two of the four bird species (European starlings, *Sturnus vulgaris*, [12] and thin billed prions, *Pachyptila belcheri* [11], the authors determined that leptin did not function as an adipostat. In the remaining two bird species (Adele penguins, *Pygoscelis adeliae*, and Bartailed Godwits, *Limosa lapponica*) [15], while seasonal changes in body mass were observed, leptin was not biochemically detected in either species. In the Eastern fence lizard (*Sceloporus undulates)*, while Spanovich [10] observed that leptin concentrations were lowest when fat stores were at their highest in the pre-hibernation period (suggestive of a decoupling mechanism), data were unavailable to determine the relationship between fat levels and leptin at other times. Paolucci [16] observed leptin concentration in the Italian wall lizard (*Podarcis sicula*) to be highest during the reproductive quiescent period, however, adiposity was not monitored in the study. In both fish species that were reviewed (Artic Charr, *Salvelinus alpinus*) [13] and Rainbow trout (*Oncorhynchus mykiss*) [17], leptin levels were not positively correlated with body mass.

When the eutherian mammal species were categorised based on Order, diet, whether or not the species hibernates, and whether or not the species is a long- or short-day breeder, there was no grouping where leptin functioned as an adipostat in all species of that particular category (Table 2 & 3). As the adipostatic function of leptin was not observed in non-eutherian mammals, reptiles, birds and fish, these groups were not included in this categorisation.

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Table 1. Data extracted from each study including species taxonomic information, number of animals included in the study and sex, whether or not there was evidence that leptin functions as an adipostat, whether there was evidence for leptin decoupling or sensitivity, the method of fat determination used and whether this was validated (if necessary), and study duration.

Author (year)	Taxa	Order	Species (Scientific name)	No. of animals	Sex	Evidence that leptin indicates adiposity?	Evidence of leptin decoupling or sensitivity?	Fat determination method (validated? Y/N)	Study duration
Soppela et al. (2008)	Mammal (eutherian)	Artiodactyla	Reindeer (*Rangifer tarandus*)	16	M	Yes	Yes	Body mass (N)	4.5 months
(Spady et al., 2009)	Mammal (eutherian)	Carnivora	American Black Bear (*Ursus americanus*)	20	M & F	Yes	No	Body fat % (NA)	6 months
Fuglei et al. (2004)	Mammal (Placental)	Carnivora	Arctic fox (*Alopex lagopus*)	8	M	No	No	Body mass (N)	6 months
Arnould et al. (2002)	Mammal (Placental)	Carnivora	Antarctic fur seal (*Arctocephalus gazelle*)	28	M & F	No	No	Body mass (Y)	3-5 days
(Nieminen et al., 2001)	Mammal (Placental)	Carnivora	Blue fox *(Vulpes lagopus)*	11	M & F	Yes	Yes	BMI (N)	6 months
Mustonen et al. (2005)	Mammal (Placental)	Carnivora	Blue fox *(Vulpes lagopus)*	48	M & F	Yes	Yes	BMI (Y)	12 months
Hissa et al. (1998)	Mammal (Placental)	Carnivora	European Brown bear (*Ursus arctos arctos*)	6	M & F	Yes	No	Fat reserves (NA)	12 months
Tauson et al. (2002)	Mammal (Placental)	Carnivora	Mink (*Neovison vison*)	6	F	Yes	No	Body mass (N)	2 months
Nieminen et al. (2000)	Mammal (eutherian)	Carnivora	Mink (*Neovison vison*)	53	F	No	No	BMI (N)	5 months

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Author (year)	Taxa	Order	Species (Scientific name)	No. of animals	Sex	Evidence that leptin indicates adiposity?	Evidence of leptin decoupling or sensitivity?	Fat determination method (validated? Y/N)	Study duration
(Ortiz, Noren, et al., 2001)	Mammal (Placental)	Carnivora	Northern Elephant Seal (*Mirounga angustirostris*)	40	M & F	No	No	Fat mass (NA)	Unclear
(Ortiz, Wade, et al., 2001)	Mammal (Placental)	Carnivora	Northern Elephant Seal (*Mirounga angustirostris*)	15	M & F	No	No	Body mass (N)	7 weeks
Kitao et al. (2011)	Mammal (Placental)	Carnivora	Racoon dog (*Nyctereutes procyonoides*)	9	M & F	Yes	Yes	Body fat % (NA)	8 months
Nieminen et al. (2004)	Mammal (Placental)	Carnivora	Racoon dog (*Nyctereutes procyonoides*)	11	M & F	Yes	Yes	BMI (N)	6 months
Nieminen et al. (2002)	Mammal (Placental)	Carnivora	Racoon dog (*Nyctereutes procyonoides*)	33	M & F	Yes	Yes	Body mass (Y)	6 months
Srivastava and Krishna (2008)	Mammal (Placental)	Chiroptera	Greater Asiatic yellow bat (*Scotophilus heathi*)	120	F	Yes	No	Fat Content & body mass (NA)	12 months
Banerjee et al. (2011)	Mammal (Placental)	Chiroptera	Indian short-nosed fruit bat (*Cynopterus sphinx*)	72	F	Yes	No	Body fat content & body mass (NA)	12 months

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Author (year)	Taxa	Order	Species (Scientific name)	No. of animals	Sex	Evidence that leptin indicates adiposity?	Evidence of leptin decoupling or sensitivity?	Fat determination method (validated? Y/N)	Study duration
Banerjee et al. (2010)	Mammal (Placental)	Chiroptera	Indian short-nosed fruit bat (*Cynopterus sphinx*)	76	F	Yes	No	Body fat content & body mass (NA)	10 months
Widmaier et al. (1997)	Mammal (Placental)	Chiroptera	Little Brown Bat (*Myotis lucifugus*)	Unclear	F	No	No	Fat index (fat mass/lean dry mass) (NA)	1 month
Kronfeld-Schor et al. (2000)	Mammal (Placental)	Chiroptera	Little Brown Bat (*Myotis lucifugus*)	Unclear	F	Unclear	Yes	Body fat & body mass (NA)	2 months
Roy and Krishna (2010)	Mammal (Placental)	Chiroptera	Greater asiatic yellow bat (*Scotophilus heathi*)	Unclear	M	Yes	No	Body fat content & body mass (NA)	12 months
Srivastava and Krishna (2007)	Mammal (Placental)	Chiroptera	Greater asiatic yellow bat (*Scotophilus heathi*)	Unclear	F	Yes	No	Body fat content & body mass (NA)	6 months
Wang et al. (2006c)	Mammal (Placental)	Lagomorphs	Pikas (*Ochotona curzoniae*)	40	M & F	Yes	NR	Body fat content &	9 months

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Author (year)	Taxa	Order	Species (Scientific name)	No. of animals	Sex	Evidence that leptin indicates adiposity?	Evidence of leptin decoupling or sensitivity?	Fat determination method (validated? Y/N)	Study duration
								body mass (NA)	
Garcia et al. (2011)	Mammal (Placental)	Primate	Japanese macaques (*Macaca fuscata)*	14	F	No	No	BMI (N)	2 months
Whitten and Turner (2008)	Mammal (Placental)	Primate	Vervet Monkeys (*Chlorocebus pygerythrus)*	116	M & F	No	No	BMI (Y)	12 months
Li and Wang (2005)	Mammal (Placental)	Rodent	Brandt's Voles *Microtis Brandti*	Unclear	Unclear	Yes	No	Body fat content & body mass (NA)	5 months
Zhang and Wang (2006)	Mammal (Placental)	Rodent	Brandts voles (*Microtis Brandti*)	16	M & F	Yes	No	Body fat content & body mass (NA)	4 weeks
Zhang and Wang (2006)	Mammal (Placental)	Rodent	Brandts voles (*Microtis Brandti)*	50	M	Yes	No	Body fat content & body mass (NA)	8 weeks
Xing et al. (2015)	Mammal (Placental)	Rodent	Daurian Ground Squirrel (*Spermophilus dauricus*)	Unclear	F	Yes	Yes	Body fat content & body mass (NA)	8 months

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Author (year)	Taxa	Order	Species (Scientific name)	No. of animals	Sex	Evidence that leptin indicates adiposity?	Evidence of leptin decoupling or sensitivity?	Fat determination method (validated? Y/N)	Study duration
Chen et al. (2012)	Mammal (Placental)	Rodent	Maximowiczi's voles (*Microtus maximowiczii*)	Unclear	Unclear	Yes	No	Body fat content & body mass (NA)	8 months
Zhang and Wang (2007)	Mammal (Placental)	Rodent	Mongolian gerbils (*Meriones unguiculatus*)	75	M & F	Yes	Yes	Body fat content & body mass (NA)	12 months
Wang et al. (2006b)	Mammal (Placental)	Rodent	Root voles (*Microtus oeconomu)*	10	M & F	Yes	No	Body fat content & body mass (NA)	10 months
Wang et al. (2006a)	Mammal (Placental)	Rodent	Root voles (*Microtus oeconomu)*	20	M & F	Yes	No	Body fat content & body mass (NA)	4 weeks
Schradin et al. (2014)	Mammal (Placental)	Rodent	Striped mice (*Rhabdomys pumilio*)	Unclear	M & F	No	Yes	Body mass (N)	12 months
Zhao (2011)	Mammal (Placental)	Rodent	Striped hampsters (*Cricetulus barabensis*)	64	Unclear	No	No	Body fat content & body mass (NA)	3 months

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Author (year)	Taxa	Order	Species (Scientific name)	No. of animals	Sex	Evidence that leptin indicates adiposity?	Evidence of leptin decoupling or sensitivity?	Fat determination method (validated? Y/N)	Study duration
Zhao et al. (2014)	Mammal (Placental)	Rodent	Striped hampsters (*Cricetulus barabensis*)	52	M	No	No	Body fat	3 months
Florant et al. (2004)	Mammal (Placental)	Rodent	Yellow bellied marmot (*Marmota flaviventris*)	7	M & F	Yes	Yes	Body fat & body mass (NA)	12 months
Sprent et al. (2012)	Mammal (prototherian)	Monotremata	Short beaked echidna (*Tachyglossus aculeatus*)	34	M & F	No	Yes	Lean body mass (N)	36 months
Yosefi et al. (2010)	Avian	Charadriiformes	Bar-tailed Godwit (*Limosa lapponica*)	Unclear	M & F	No	NA	Correlation of body fat mass, body mass & wing length (Y)	On arrival at landing site
Yosefi et al. (2010)	Avian	Sphenisciformes	Adele penguin (*Pygoscelis adeliae*)	Unclear	M & F	No	NA	Isotope dilution approach (NA)	Pre-incubation and 45 days post egg laying
Kordonowy et al. (2010)	Avian	Passiferormes	European starling (*Sturnus vulgaris*)	57	F	No	No	Body fat & body mass (NA	4 months

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Author (year)	Taxa	Order	Species (Scientific name)	No. of animals	Sex	Evidence that leptin indicates adiposity?	Evidence of leptin decoupling or sensitivity?	Fat determination method (validated? Y/N)	Study duration
Quillfeldt et al. (2009)	Avian	Procellariiformes	Thin billed prion (Pachyptila belcheri)	Unclear	Unclear	No	No	Body condition (N)	5 months
Spanovich et al. (2006)	Reptile	Squamata	Eastern fence lizard (Sceloporus undulatus)	60-180	M & F	Unclear	Yes	Fat Stores (NA)	12 months
Paolucci et al. (2001)	Reptile	Squamata	Italian wall lizard (Podarcis sicula)	Unclear	F	Unclear	NA	Fat body mass (NA)	9 months
Froiland et al. (2012)	Fish	Salmoniformes	Arctic charr (Salvelinus alpinus)	230	M & F	No	No	Body fat & body mass (NA	9 months
(Salmeron et al., 2015)	Fish	Salmoniformes	Rainbow trout (Oncorhynchus mykiss)	92	Unclear	No	No	Adipose Tissue mass (NA)	8 WEEKS

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Table 2. Species specific data collected from each study including species diet category, whether wild or captive, mature or immature, long- or short- day breeders and whether the species hibernates or migrates.

Author (year)	Species	Diet	Mature or immature	Long- or short-day breeder	Hibernate or migrate
Soppela et al. (2008)	Reindeer	Herbivore	Immature	Long	No
Spady et al. (2009)	American Black Bear	Omnivore	Mature	Long	Yes
Fuglei et al. (2004)	Arctic fox	Carnivore	Mature	Long	No
Arnould et al. (2002)	Antarctic fur seal	Carnivore	Both	Long	No
Nieminen et al. (2001)	Blue fox	Omnivore	Mature	Short	No
Mustonen et al. (2005)	Blue fox	Omnivore	Mature	Short	No
Hissa et al. (1998)	European Brown bear	Omnivore	Mature	Long	Yes
Tauson et al. (2002)	Mink	Carnivore	Mature	Short	No
Nieminen et al. (2000)	Mink	Carnivore	Mature	Short	No
Ortiz et al. (2001)	Northern Elephant Seal	Carnivore	Immature	Short	No
Kitao et al. (2011)	Racoon dog	Omnivore	Mature	Long	Yes
Nieminen et al. (2004)	Racoon dog	Omnivore	Immature	Long	Yes
Nieminen et al. (2002)	Racoon dog	Omnivore	Immature	Long	Yes
Srivastava et al. (2008)	Greater Asiatic yellow bat	Insectivorous	Mature	Long	Yes
Banerjee et al. (2011)	Indian short-nosed fruit bat	Frugivore	Mature	Long	Yes
Banerjee et al. (2010)	Indian short-nosed fruit bat	Frugivore	Mature	Long	Yes
Widmaier et al. (1997)	Little Brown Bat	Insectivorous	Mature	Long	Yes
Townsend et al. (2008)	Little Brown Bat	Insectivorous	Mature	Long	Yes
Kronfeld-Schor et al. (2000)	Little Brown Bat	Insectivore	Mature	Long	Yes
Roy et al. (2010)	Greater asiatic yellow bat	Insectivorous	Mature	Long	Yes
Srivastava et al. (2007)	Greater asiatic yellow bat	Insectivorous	Mature	Long	Yes
Wang et al. (2006)	Pikas	Herbivore	Mature	Long	No
Garcia et al. (2011)	Japanese macaques	Omnivore	Mature	Short	No
Garcia et al. (2010)	Japanese macaques	Omnivore	Mature	Short	No
Whitten et al. (2008)	Vervet Monkeys	Herbivore	Mature	Long	No
Li et al. (2005)	Brandt's Voles	Omnivore	Unclear	Long	No
Zhang et al. (2006)	Brandts voles	Omnivore	Mature	Long	No
Xing et al. (2015)	Daurian Ground Squirrel	Herbivore	Mature	Long	Yes
Chen et al. (2012)	Maximowiczi's voles	Herbivore	Mature	Long	No

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Zhang et al. (2007)	Mongolian gerbils	Herbivore	Mature	Long	No
Wang et al. (2006)	Root voles	Omnivore	Mature	Long	No
Wang et al. (2006)	Root voles	Omnivore	Mature	Long	No
Schradin, et al. (2014)	Striped mice	Omnivore	Mature	Long	No
Zhao et al. (2011)	Striped hamsters	Omnivore	Mature	Long	Yes
Zhao et al. (2014)	Striped hamsters	Omnivore	Mature Mature	Long	Yes
Florant et al. (2004)	Yellow bellied marmot	Herbivore		Long	Yes
Sprent et al. (2012)	Short beaked echidna	Insectivorous	Mature	Short	Yes
Yosefi et al. (2010)	Bar-tailed Godwit	Omnivore	Mature	Unclear	Yes
Yosefi et al. (2010)	Adele penguin	Carnivore	Mature	Long	Yes
Kordonowy et al. (2010)	European starlings	Omnivore	Immature	Long	Yes
Quillfeldt et al. (2009)	Thin billed prions	Carnivore	Immature	Long	Yes
Spanovich, et al. (2006)	Eastern fence lizard	Insectivorous	Mature	Long	Yes
Paolucci et al. (2001)	Italian wall lizard	Insectivorous	Mature	Long	Yes
Froiland et al. (2012)	Arctic charr	Insectivore	Immature	Long	No
Salmeron, et al. (2015)	Rainbow trout	Carnivore	Mature	Long	No

Table 3. Eutherian mammal species identified in the literature search categorised by Order, diet, whether or not the species hibernates and whether or not the species is a long- or short-day breeder.

		Does leptin signal adiposity?		
Category	**No. species in group**	**Yes (%)**	**No (%)**	**Unclear (%)**
Order				
Carnivora	8	4 (50)	3 (37)	1 (12)
Chiprotera	4	3 (75)	1 (25)	0
Rodent	8	5 (63)	3 (37)	0
Primate	4	2 (50)	2 (50)	0
Diet				
Herbivore	6	4 (67)	2 (33)	0
Insectivore	2	1 (50)	1 (50)	0
Carnivore	4	0	3 (75)	1 (25)
Omnivore	9	6 (67)	3 (33)	0
Hibernating species	9	7 (78)	2 (22)	0

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Timing of breeding season				
Long-day	19	13 (68)	6 (32)	0
Short-day	5	1 (20)	3 (60)	1(20)

4. Discussion

The aim of this systematic review was to determine if the adipostatic function of leptin is conserved across taxa, or if as speculated by Sprent [8], it is restricted to therian or eutherian mammals. This review identified numerous studies investigating eutherian mammals, however, there was a paucity of literature investigating sub-eutherian mammals, birds, reptiles and fish. While the few studies investigating these less represented groups failed to identify a relationship between leptin and adiposity, it is important to consider the limitations of these studies before concluding that no relationship exists. Surprisingly, the adipostatic function of leptin was not observed in all eutherian species investigated, suggesting species-specific functionality. These findings are discussed here, highlighting limitations of the included studies.

4.1. Sub-Eutherian Mammals and Reptiles—Further Research Required

While Sprent [8] did not observe a relationship between leptin and adiposity in the short-beaked echidna, there are two major caveats to consider. First, their study was conducted on the Tasmanian sub-species of short-beaked echidna which demonstrates unique peculiarities compared to the other four sub-species. For example, due to the cooler Tasmanian climate, this sub-species maintains hibernation for extended periods in comparison to those from milder climates (e.g., South-East Queensland and Kangaroo Island populations), so much so, that hibernation and reproductive activity reportedly overlap, a phenomenon not witnessed in the other sub-species [18]. Although a eutherian species, Weitten, Robin [19] has reported that the Siberian hamster showed decreased levels of circulating leptin concentrations during hibernation. Consequently, the extended hibernation period observed in the Tasmanian sub-species of short-beaked echidna could potentially confound the correct interpretation of the relationship between adiposity and leptin in this sub-species, such that extrapolation to the remaining sub-species may be problematic.

Secondly, Sprent [8] did not measure adiposity directly, but instead used body mass as a proxy measure. While body mass is a reasonable alternative given the cost associated with specialised equipment (e.g., duel-energy x-ray absorptiometry (DEXA) scans) or ethical concerns associated with sacrificing study animals to determine their fat composition [20], the literature suggests that body mass does not always reflect body fat levels [21]. For example, Zhao [22] reported that striped hamsters maintained constant body mass between seasons while body fat composition fluctuated. Similarly, Spady [23] showed that body mass and body condition index were not as accurate as leptin itself in monitoring adiposity in the American Black Bear. Consequently, the results reported by Sprent [8] need to be interpreted with caution and further investigation into the adipostatic function of leptin in echidnas and other sub-eutherian mammals is required.

Since the publication of the Sprent [8] study, new evidence has emerged supporting an adipostatic role of leptin in *Tachyglossus aculeatus*. In a study of captive short-beaked echidnas housed under non-breeding conditions, Dutton-Regester [24] demonstrated a significant positive correlation between circulating leptin levels and directly measured body fat percentage using dual-energy X-ray absorptiometry (DEXA). This represents the first robust evidence that leptin may function as an adipostat in a monotreme species, suggesting that this mechanism could be evolutionarily conserved beyond eutherian mammals. Notably, no sex differences in leptin concentrations were observed despite females having higher body fat, indicating a possible divergence from patterns seen in some therian species. Furthermore, no seasonal variation in leptin levels was detected in the study cohort, though this may reflect the buffered environmental conditions of captivity. These findings warrant further investigation in wild echidna populations and other sub-eutherian taxa to assess seasonal and environmental influences on leptin signalling.

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In reptiles, Spanovich, Niewiarowski [10] and Paolucci, Rocco [25] have provided evidence that leptin may function as an adipostat in the Eastern Fence lizard and the Italian Wall lizard, respectively. While there was insufficient information presented to determine the relationship between circulating leptin concentrations and adiposity outside of the hibernation period in the Eastern Fence lizard, Spanovich [10] did observe leptin decoupling during the hibernation period. Therefore, it is quite possible that at other times of the year, leptin may signal adiposity as it does in many hibernating eutherian mammals that demonstrate this phenomenon [26,27]. In the Italian wall lizard, while adiposity was not monitored by Paolucci, Rocco [25], the authors refer to a previous study [28] where fat bodies were largest during the quiescent period of the reproductive cycle, corresponding to the period of high leptin concentration reported by Paolucci, Rocco [25].

4.2. Birds and Fish – Evidence for No Adipostatic Function

Prior to 2014 there had been long-standing contention surrounding the presence of leptin in birds. However, since 2014 avian *leptin* has been identified in the genomes of various avian species including falcons (*Falco peregrinus* and *Falco cherrug*), Tibetan ground tit (*Pseudopodoces humilis*), zebra finch (*Taeniopygia guttata*), rock dove (*Columba livia*), bald eagle (*Haliaeetus leucocephalus*), downy woodpecker (*Picoides pubescens*), budgerigar (*Melopsittacus undulatus*), duck (*Anas platyrhynchos)* and chicken (*Gallus gallus) [3].* These avian leptin sequences have significantly higher guanine-cytosine content compared to other vertebrates, low sequence conservation with mammalian leptin and low level of expression; all of which precluded the identification of avian leptin for so long [3]. Given this lack of conservation, it is not surprising that Yosefi, Hen [15] were unable to detect biologically relevant levels of leptin in the Adele penguin and the Bar-tailed godwit. While Kordonowy [12] and Quillfeldt [11] have reported leptin concentrations for the European starling and the thin-billed prion, respectively, it is likely that these studies were based on reagents that were developed using leptin sequences with more than 95% similarilty to mouse leptin [3]. Consequently, it would be interesting to repeat these studies using the appropriate reagent to ascertain the true relationship, if any, between leptin and adiposity in these species.

Despite these findings, there is also evidence to suggest that leptin may not function as an adipostat in birds. For example, there is high correlation between leptin and leptin receptor transcript in birds, suggesting that leptin may not circulate but rather function as an autocrine or paracrine factor [29]. Further, while leptin is almost exclusively expressed in the adipose tissue of mammals, it is almost undetectable in the adipose tissue of avian species [30,31]. Instead, it is largely expressed in the liver. This hepatic expression is likely associated with the primary role that the liver plays in vitellogenesis in avian species [30].

Similar to birds, there is strong evidence that leptin does not signal adiposity in fish. First, as is the case for birds, the liver is the primary tissue of leptin expression in fish [32]. Second, many observations in fish species run counter to the adipostatic model proposed in mammals. For example, plasma leptin concentrations increase with fasting in salmonids [17] and flounder [33], and even when offered food, Arctic Charr stop feeding when leptin titres fall but eat during periods of rising leptin concentrations. Finally, the ancestral leptin giving rise to leptins in birds, reptiles, and mammals is more closely related to coelacanth and shark (*Callorhinchus milii*) leptins than leptins from bony fish, i.e., fish leptins appear to have diverged along their own lineage independent of leptins in higher mammals [34].

4.3. Eutherian Mammals – Evidence for Species-Specific Functionality

While leptin is commonly referred to as an adipostat in eutherian mammalian species [2], the results of this systematic review have revealed that this is not a universal phenomenon, with several species including the Arctic Fox, Antarctic Fur seal, Northern elephant seal, Little brown bat, Japanese macaque, Vervet monkey, European beaver, Striped mouse and the Striped hamster all failing to demonstrate a relationship between adiposity and circulating leptin levels. In some cases, the lack of this relationship may be attributed to deficiencies in study design. For example, studies on the

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Northern elephant seal [35], Vervet monkey [21] and the Striped mouse [36] all failed to use a validated proxy measure for body fat, while the study on the Antarctic fur seal [37] suggested that suckling of young or a post exercise response may have confounded their results. Nevertheless, it is unclear why the adipostatic function of leptin was not observed in the remaining species.

Some authors have suggested that the adipostatic function of leptin is absent in carnivorous species [38,39]. However, this was not evident in this review, as four of the eight carnivorous species identified demonstrated a positive correlation between leptin and adiposity. Additionally, in two separate studies on the mink, while Niemenen [39] found leptin did not signal adiposity, a later study by Tauson [14] contradicted this finding. While the reason for this difference is unclear, Tauson [14] exposed minks to a variable food supply with plasma leptin concentrations mirroring body weight lost and gain as food was restricted or increased, respectively. Further, having previously demonstrated that plasma insulin levels change in response to energy supply, Tauson [14] demonstrated plasma leptin and insulin concentrations followed the same pattern, providing further evidence that leptin signals adiposity in the carnivorous mink.

Irrespective of whether the eutherian mammal species identified in this review were grouped according to Order, diet, long- or short- day breeder, and whether they hibernate or migrate, there was no single group category whereby leptin functioned as an adipostat (or vice versa) in all species. Thus, as non-seasonal mammals have not been included in this review, it is hypothesised that in seasonal eutherian mammals, the adipostatic function of leptin is species-specific. As Zhao [22] explains, there may be species-specific physiological and hormonal control of body mass and adiposity which may be linked to species-specific responses to seasonal changes in temperature, photoperiod or food availability.

5. Conclusions

The objective of this review was to determine if the adipostatic function of leptin was conserved across the vertebrate taxa, with a focus on seasonally reproducing vertebrates. Few studies have investigated sub-eutherian mammals (with a complete lack of research on marsupial mammals), birds, reptiles or fish; therefore, it was not possible to reach a definitive conclusion regards our original question. Nevertheless, current evidence would suggest that the adipostatic function of leptin is absent in avian and fish species. More research is necessary before conclusions can be drawn for sub-eutherian and reptilian species as the presented results were inconclusive. Surprisingly, the adipostatic function of leptin was also not observed in all eutherian species investigated, leading to a conclusion of species-specific functionality which we suggest may extend to sub-eutherian mammals and reptiles.

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Abbreviations

The following abbreviations are used in this manuscript:

DEXA Duel-Energy X-ray Absorptiometry

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