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Received: 11 September 2024 | Accepted: 11 September 2024

DOI: 10.1111/age.13476

REVIEW

ANIMAL GENETICS WILEY

The role of G protein-coupled receptors and their ligands in animal domestication

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Funding information
European Union – NextGenerationEU, Grant/Award Number: PRIN2022JLA3EA; Deutsche Forschungsgemeinschaft, Grant/Award Number: 221545957, 390540038 and 421152132; Vetenskapsrådet, Grant/Award Number: 2017-02907; European Union's Horizon 2020 - MSCA, Grant/Award Number: 956314; Knut and Alice Wallenberg Foundation, Grant/Award Number: KAW 2016.0361

Abstract

The domestication of plants and animals has resulted in one of the most significant cultural and socio-economical transitions in human history. Domestication of animals, including human-supervised reproduction, largely uncoupled particular animal species from their natural, evolutionary history driven by environmental and ecological factors. The primary motivations for domesticating animals were, and still are, producing food and materials (e.g. meat, eggs, honey or milk products, wool, leather products, jewelry and medication products) to support plowing in agriculture or in transportation (e.g. horse, cattle, camel and llama) and to facilitate human activities (for hunting, rescuing, therapeutic aid, guarding behavior and protecting or just as a companion). In recent years, decoded genetic information from more than 40 domesticated animal species have become available; these studies have identified genes and mutations associated with specific physiological and behavioral traits contributing to the complex genetic background of animal domestication. These breeding-altered genomes provide insights into the regulation of different physiological areas, including information on links between e.g. endocrinology and behavior, with important pathophysiological implications (e.g. for obesity and cancer), extending the interest in domestication well beyond the field. Several genes that have undergone selection during domestication and breeding encode specific G protein-coupled receptors, a class of membrane-spanning receptors involved in the regulation of a number of overarching functions such as reproduction, development, body homeostasis, metabolism, stress responses, cognition, learning and memory. Here we summarize the available literature on variations in G protein-coupled receptors and their ligands and how these have contributed to animal domestication.

KEYWORDS
animal domestication, G protein-coupled receptor, GPCR variants, molecular evolution

INTRODUCTION

Domestication of animals is a complex process that has resulted in animals with improved desirable traits (from a human perspective). It has affected a broad range of phenotypic traits including life history and reproduction (to control photoperiodic reactions, fertility and mating behavior), diet and metabolism (to increase e.g. meat, milk, honey, leather production and muscle strength), behavior and cognition (to modify sensory perception, social and aggressive behaviors; Driscoll et al., 2009; Hecht et al., 2023; Wang et al., 2014). In this context, the term domestication can be used to define species that have become dependent

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through the active management of the domesticator. However, the initial phases of domestication could arise without intentional behavior on the part of the proto-domesticator: the commensal hypothesis posits that domestication can emerge when an opportunistic species utilizes a niche created as a byproduct of another species' behavior, establishing a mutualism between two species (Zeder, 2015). Finally, it needs to be emphasized that domestication is a two-way process in which the fitness of both the domesticator and the domesticated species is altered through reciprocal interactions (Purugganan, 2022).

Domestication not only consists of the diversification of a species from its wild ancestor, but also aims to increase phenotypic variation within the domesticated species by the appearance and selection of new traits that are further promoted. It can thus be seen as a multi-step process governed by the pressure of human environment, with its peculiar needs and goals. Several aspects of 'animal-optimization' have had and still have an enormous socio-economic impact, and some will become increasingly important in the future, such as those linked to lifespan and climate tolerance, the latter being a crucial issue in agriculture already (Larson & Burger, 2013).

For humans, animal domestication started with canid domestication, whose beginning, originally estimated to occur between 16000 and 11000 years ago, is still matter of debate as more recent genomics studies indicate a much older origin, around 40000–30000 years ago (Bergstrom et al., 2020). In the Neolithic period, between 11000 and 4000 years ago, the emergence of farming promoted the domestication of other species including sheep, goats, pigs, chickens, cattle and horses (Frantz et al., 2020). Traditionally, it is believed that domestication involves an initial stage that, in animals, consists of changes in key traits including increased docility, reduced aggression and fear, and altered reproduction and coat color. A second stage involves genes that progressively optimize desirable and useful traits, contributing to the aforementioned diversification process (Herbeck & Gulevich, 2019; Schmutz & Berryere, 2007; Wang et al., 2014).

A main goal of animal genetics has been to identify the genes involved in these stages, in an attempt to retrace the geographic and temporal origin of domestication for each animal lineage and, eventually, to identify common genes and shared evolutionary strategies (Andersson & Georges, 2004; Frantz et al., 2020). As a result, a detailed picture of complex genetic mechanisms underlying domestication and related phenotypic diversity has started to be delineated, thanks to the increased capacity for genomic analyses (e.g. whole-genome sequencing, mapping, cloning, and gene isolation; Wang et al., 2014). The analysis of the genomes of many domesticated animals strongly suggests that animal domestication has a highly polygenic background with no obvious single 'domestication gene' of major importance (Andersson & Purugganan, 2022). Instead, domesticated animals evolved through the accumulation of mutations in a variety of genes that include several G protein-coupled receptors (GPCRs). The aim of this review is to highlight how changes in the genes for GPCRs and their ligands have contributed to animal domestication owing to their pivotal role in many phenotypic traits altered during domestication, such as behavior, pigmentation, metabolic regulation, circadian rhythm and reproduction.

G protein-coupled receptors are membrane-spanning proteins and form the largest group of cell surface receptors with about 830 members in human. G protein-coupled receptors and their interaction partners (e.g. ligands, G proteins and arrestins) are involved in the regulation of many physiological processes in animals and fungi (Limbird, 2004). The relevance of GPCRs (Alexander et al., 2019) is based on their key role in signal transduction from the extracellular side to the intracellular interior induced by a variety of stimuli (Hofmann et al., 2009; Kobilka & Deupi, 2007). Receptor ligand stimulants (agonists) include odors, ions, metabolites, light, nucleotides, amines, fatty acids, peptides and even larger proteins (Kristiansen, 2004). Ligand-agonist binding results in the stabilization of an active state conformation with an increased capacity for intracellular coupling and subsequent activation of e.g. G proteins or arrestins (Weis & Kobilka, 2018).

Activation of G proteins triggers activation of second messenger signaling pathways regulating ion-channel activity, cytoplasmic targets and/or gene expression (Ho et al., 2009; Veldhuis et al., 2015). G protein-coupled receptors share a common structural architecture (Figure 1) consisting of an extracellular N-terminus and an intracellular C-terminus, seven transmembrane helices connected via three intracellular and three extracellular loops, respectively. They are subdivided into five distinct classes based on specific sequence signatures (Fredriksson et al., 2003) having evolved from an ancestral gene (Nordstrom et al., 2011) very early in eukaryotic evolution (de Mendoza et al., 2014; Schoneberg et al., 2007). Malfunctions of about 100 GPCRs are associated with human disease (Hutchings et al., 2010), including viral infections, cancer, infertility, inflammation, metabolic and neurological disorders (Dorsam & Gutkind, 2007; Garcia-Jimenez & Santisteban, 2007; Schoneberg et al., 2004; Seifert & Wenzel-Seifert, 2002; Vassart & Costagliola, 2011). Owing to their essential regulatory role in physiological processes and known associations between GPCR functions, dysfunction and pathological states, these receptors are priority targets in drug development (Hauser et al., 2017; Overington et al., 2006; Sriram & Insel, 2018). Interestingly, this also includes the finding of insecticides (Liu et al., 2021; Mysore et al., 2023; Roeder, 2005), because a large number of invertebrate GPCRs exist (~200; Brody & Cravchik, 2000; Hill et al., 2002) as odorants and taste

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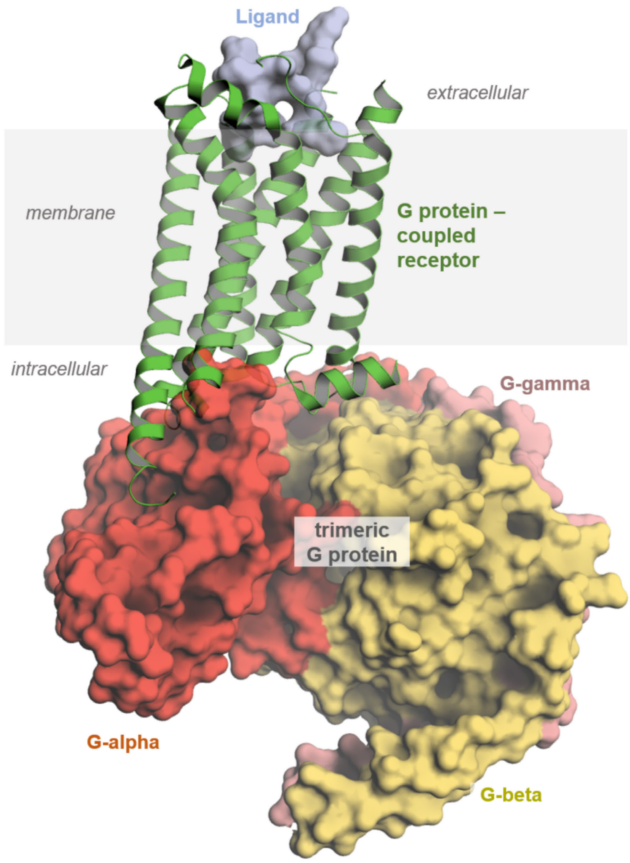

FIGURE 1 Structural complex between a class A G protein-coupled receptor (GPCR; melancortin-4 receptor, PDB ID 7piv; Heyder et al., 2021), an agonistic ligand peptide and the trimeric Gs. The ligand (surface representation, lilac) binds extracellularly and thereby modifies the receptor structure via intermolecular interactions, which consequently enables coupling and activation of the G protein hetero-trimer (surface representation) at the intracellular side. The activated G protein further stimulates second messenger signaling dependent on the G protein subtype.

receptors, opsins or aminergic receptors. Of note, insectides targeting invertebrate GPCRs can also have pathological effects on vertebrates owing to cross-reactivity with similar GPCRs (Ngai & McDowell, 2017; Van Hiel et al., 2010), and in turn, drugs (ligands) used for vertebrates can modify invertebrate GPCR functions.

G protein-coupled receptors belonging to a specific subfamily are often activated by cognate ligands that share structural similarities – as we will discuss e.g. in the case of melanocortin receptors – leading to overlapping but also very distinct functional roles. Within specific species and genders, the distribution of receptors in particular cell types and organs allows further diversification of GPCR function. A single GPCR subtype can be expressed in very different organs where it can be involved in modulating diverse responses. For example, the product of one vasopressin receptor gene (*AVPR1a*) contributes to regulating blood pressure in the blood vessels and metabolism in the liver as well as social behavior, aggression and circadian rhythms (among other functions) in the central nervous system (Koshimizu et al., 2012). Thus, it is feasible that selective mutations in a single receptor gene such as the V1a receptor can simultaneously affect several traits relevant to domestication.

We here focus on GPCRs and GPCR-ligands that are reported to be associated with domestication, such as the thyrotropin receptor (TSHR), which is involved in circadian rhythms, seasonality of reproduction, the melanocortin-4 receptor (MC4R), controlling weight gain and metabolism, the melanocortin-1 receptor (MC1R), which is responsible for coat color variations, and the vasopressin/oxytocin receptors, involved in controlling social behavior, fear and aggression (Table 1). The involvement of metabotropic glutamate receptors, a group of GPCRs involved (among other functions) in the modified stress responses observed in the hypothalamic–pituitary–adrenal axis of several domesticated species, has been extensively discussed in an excellent and exhaustive review (O'Rourke & Boeckx, 2020) and will not be further discussed here.

GPCRS AND LIGANDS INVOLVED IN BEHAVIOR CHANGES RELEVANT FOR DOMESTICATION

During the domestication process, artificial selection by humans and natural selection in the agricultural environment are expected to lead to significant changes in stress responses, aggressiveness and anxiety (Jensen, 2014). Improved quality of human–animal communication, safe interactions and non-agressiveness are indeed fundamental prerequisites for successful domestication of animals. Stress responses are regulated by two systems, the sympathetic–adrenomedullary system and the hypothalamic–pituitary–adrenal axis. G protein-coupled receptors and diverse ligands have contributed to these crucial behavioral changes (Kikusui et al., 2019). Activation of the sympathetic–adrenomedullary system via downstream projections to the adrenal medulla ultimately leads to the release of adrenaline and noradrenaline, activating the 'fight or flight' response. In parallel, the release of corticotropin-releasing hormone and arginine vasopressin (AVP) from the hypothalamus trigger secretion of the adrenocorticotropic hormone (ACTH) from the anterior pituitary, inducing the secretion of corticosteroids from the cortical medulla. The activity of the stress response systems is generally reduced in domesticated species, as suggested in an experiment carried out by Russian scientists to tame silver foxes (reviewed in Herbeck & Gulevich, 2019). In this animal-domestication model, silver foxes (*Vulpes vulpes*) underwent more than 60 years of selection, first against aggression and then in favor of an increased emotionally positive response to humans (Popova et al., 1991). Although no direct link between alteration of GPCRs and 'artificial' domestication of foxes has been reported, compelling evidence

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TABLE 1 Overview of G protein-coupled receptors (GPCRs) confirmed or suggested to be related to animal domestication.

GPCR	Animal species	Suggested phenotypical modifications	Evidence basis (causal mutations (M), genetic associations (A), expression data (E))	References
AVPR1a	Diverse species	Behavior	(A)	Fam et al. (2018)
AVPR1b	*Sus scrofa* (pig)	Meat quality, physiological changes	(A)	Terenina et al. (2013) and Fam et al. (2018)
AVPR2	Diverse species	Behavior, physiological changes	(A)	Fam et al. (2018)
CRHR1	*Gallus gallus* (chicken)	Stress responses	(E)	Lotvedt et al. (2017)
DRD3	*Sus scrofa* (pig)	Carcass composition	(A)	Terenina et al. (2013)
EDNRB	*Coturnix japonica* (Japanese quail)	Color	(M)	Miwa et al. (2007)
	Gallus gallus domesticus	Color	(M)	Kinoshita et al. (2014)
GPR126 (*ADGRG6*)	*Sus scrofa* (pig)	Body length, diverse others	(A)	Li et al. (2014)
GPR176	*Bos taurus* (Hanwoo)	Unknown (circadian behavior?)	(A)	Lee et al. (2013)
HTR1B	*Bos taurus* (bovine)	Milk production	(M)	Zhang et al. (2008)
HTR3C	*Bos taurus* (bovine)	Milk production	(A)	Korkuc et al. (2023)
HTR4	*Canis lupus familiaris* (dog)	Behavior	(E)	Li et al. (2013)
MC1R	*Equus caballus* (horse)	Color	(M	Marklund et al. (1996)
	Canis lupus familiaris (dog)	Color	(M)	Kaelin and Barsh (2013)
	Sus scrofa (pig)	Color	(M)	Andersson (2003)
	Anas platyrhynchos (Jianchang duck)	Color	(M)	Wang et al. (2020)
	Gallus gallus (chicken)	Color	(M)	Andersson et al. (2020)
	Bos taurus (cattle)	Color	(M)	Ji and Tao (2022)
	Felis catus (cat)	Color	(M)	Gustafson et al. (2017)
	Oryctolagus cuniculus (rabbit)	Color	(M)	Fontanesi et al. (2006)
MC3R	*Gallus gallus* (chicken)	Production traits	(M)	Sharma et al. (2008) and Zhang et al. (2021)
MC4R	*Sus scrofa* (pig)	Fatness, growth	(A), (M)	Kim et al. (2000)
	Bos taurus (Madrasian cattle)	Improved growth	(A)	Utomo et al. (2021)
	Gallus gallus (chicken)	Body weight	A)	Kubota et al. (2019)
RXFP2 (*LGR8*)	*Ovis aries* (Chinese sheep)	Horn phenotype (semi-feralization)	(A)	Pan et al. (2018)
	Ovis ammon (Tibetian sheep)	Horn phenotype	(M)	Hu et al. (2019)
TAS2R5	*Canis dingo* (dingo)	Perception of bitterness (domestication and/or feralization)	(A)	Zhang et al. (2020)
TAS2R	*Sus scrofa* (pig)	Plastic trait	(A)	da Silva et al. (2014)

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TABLE 1 (Continued)

GPCR	Animal species	Suggested phenotypical modifications	Evidence basis (causal mutations (M), genetic associations (A), expression data (E))	References
TSHR	*Gallus gallus* (chicken)	Reproductive seasonality	(E)	Rubin et al. (2010) and Fallahshahroudi et al. (2021)
	Capra aegagrus hircus (goat)	Reproductive seasonality	(M)	Signer-Hasler et al. (2022)
	Anser (geese)	Flightlessness of domesticated geese	(A)	Peng et al. (2018)

for a reduction in ACTH and cortisol plasma levels and blunted adrenal reactivity were present in tamed foxes as compared to wild-type controls (Rosenfeld et al., 2020). Interestingly, a crossbreeding study using a similar domestication model for rats revealed a highly significant quantitative trait locus affecting both tameness and the size of the adrenal gland (Albert et al., 2009).

Vasopressin and oxytocin receptors

The vasopressin receptor (AVPR) and oxytocin receptor (OTR) belong to the same GPCR subfamily, as they share high sequence identity and bind the highly related peptides oxytocin (OT) and AVP, which are structurally related cyclic nona-peptides synthesized in the same hypothalamic nuclei (Rae et al., 2022). These two neuropeptides and their receptors play a crucial role in shaping social behavior as they regulate empathy, social motivation, social anxiety, pair bonding, affiliation and group cooperation, representing candidate genes possibly involved in domestication (Herbeck & Gulevich, 2019). A study that revealed a dynamic scenario in which the OTR was found to be under evolutionary constraint in placental mammals, while the vasopressin receptors AVPR1a, AVPR1b and AVPR2 exhibited accelerated rates of evolution (Pare et al., 2016), led to the hypothesis that amino acid changes in these receptors could be associated with animal domestication. Specific sites in AVPR1b and AVPR2 genes that are under positive selection were indeed identified, supporting the hypothesis that they could be involved in behavior and physiological changes related to domestication (Fam et al., 2018). In addition, the AVPR1a subtype was found to be under relaxed selective constraint in domesticated species (Fam et al., 2018). It is noteworthy that OT binds to the OTR, whose involvement in domestication has also been investigated in a few studies, but definitive evidence for OTR involvement in the context of domestication/breeding has not yet been provided (Herbeck & Gulevich, 2019).

Serotonin receptors

In a comparative study of wolves and Chinese native dogs, a highly differentiated genomic region containing the serotonin receptor-4 (HTR4) gene was identified (Li et al., 2013). Altered expression of other serotonin receptor subtypes (HTR1A and HTR2C) was reported for tame foxes and rats in different brain regions including the hypothalamus (Kukekova et al., 2011; Popova et al., 2010).

Corticotropin releasing hormone receptor 1

The corticotropin releasing hormone receptor 1 (*CRHR1*) gene has been suggested to be associated with

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chicken domestication (Lotvedt et al., 2017). Expression of a panel of genes in five tissues known for their involvement in the stress response (hippocampus, hypothalamus, pituitary, adrenal glands and liver) of domesticated white Leghorn chickens was investigated and compared with the wild ancestor of domesticated breeds, the Red Junglefowl. The authors reported a decrease in expression of *CRHR1* in the pituitary gland of chickens after stress, which can be involved in negative feedback regulation of the stress response and, thereby, explain the attenuated stress response in the domesticated birds. However, here a causal relationship between changes in gene expression and an altered stress response needs further validation.

Finally, many studies have suggested behavior-associated genes including GPCRs (Table 1) that may be involved in the domestication of different species. However, it has been difficult to find conclusive evidence for specific genetic changes in GPCR switches that have led to behavioral change in domesticated animals. The most likely explanation is that animal domestication has a highly polygenic background, in which allele frequency changes at many loci with small effects dominate (Carneiro et al., 2014).

GPCRS AND LIGANDS INVOLVED IN MORPHOLOGICAL CHANGES

Pigmentation

One of the most characteristic phenotypic changes in domesticated animals concerns hair (Cieslak et al., 2011) and feather pigmentation. It has been argued that changes in pigmentation are a by-product of selection for tameness assuming that some genes affect both neural development and pigmentation (Wilkins et al., 2014). However, no conclusive evidence supporting this speculation has been reported yet. It is more likely that the most important reason for the extensive diversity in pigmentation among domestic animals is direct diversifying selection on genes affecting pigmentation (Fang et al., 2009). The reason is that humans care about the appearance of their domestic animals, and a novel coat or feather color variant is likely to be maintained and spread unless it is associated with an obvious defect like poor vision or hearing.

Melanocortin-receptor 1 and agouti-signaling protein

The most common pathway affecting pigmentation in domestic animals involves the G protein-coupled receptor MC1R and the interaction with agouti-signaling protein (ASIP). MC1R signaling is stimulated by the ligands α- and β-melanocyte-stimulating hormones (MSH, melanotropin) both derived from pro-opiomelanocortin (POMC), while ASIP blocks MC1R activation (Lu et al., 1994). MC1R–ASIP interaction determines pigment switching, whereby MC1R signaling activates the synthesis of black/brown eumelanin, while MC1R inactivation owing to the action of ASIP causes the production of red/yellow pheomelanin. Pigmentation in most animals involves a combination of both eumelanin and pheomelanin. *MC1R* mutations occur in most, if not all, domestic animals (Cieslak et al., 2011). The reason why *MC1R* mutations are common, both in domestic and wild animals, is possibly that mutations in this gene do not cause negative pleiotropic effects on other traits.

Loss-of-function mutations in *MC1R* are recessive and cause pure red/yellow pheomelanin pigmentation, whereas mutations causing constitutive activation of MC1R signaling show dominant inheritance and are associated with black/brown mutation. In many species an *MC1R* allelic series occurs. One example is the pig where alleles are present with the following order of dominance: dominant black (E^D), wild-type (E^+), black spotting (E^p) and recessive yellow (e) (Kijas et al., 2001). The black-spotting allele is particularly interesting since it is due to the combination of two different mutations. One is a missense mutation (Leu99Pro) causing the dominant black color and the other is a 2 bp insertion in codon 23 causing a frameshift and complete inactivation. Thus, the expected phenotype of E^p/E^p homozygotes is red color. However, the 2 bp insertion is somatically unstable and frequently reverts to the wild-type sequence, under which circumstances the dominant black mutation is reactivated, causing black spots (Kijas et al., 2001).

ASIP mutations also occur in many domestic animals but are not as common as *MC1R* mutations. Compared with *MC1R*, *ASIP* mutations show the opposite trend to that expected because ASIP is an antagonist to MC1R. Thus, inactivating mutations in *ASIP* cause recessive black, eumelanin pigmentation, whereas gain-of-function may cause a dominant white/yellow color. An example of the former case is recessive black color in horses caused by homozygosity for an 11 bp deletion in *ASIP* exon 2 leading to a frameshift (Rieder et al., 2001). In contrast, a 190 kb duplication encompassing *ASIP* leads to upregulated ASIP expression causing a dominant white/tan color in sheep (Norris & Whan, 2008).

Endothelin receptor type B and its ligand endothelin-3

Endothelin receptor type B (EDNRB) is another GPCR with a critical role in pigmentation biology. EDNRB and its interaction with the ligand endothelin-3 (EDN3) is crucial for melanocyte proliferation and migration (Cieslak et al., 2011). However, EDNRB

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function is also critical for the development of nerves of the intestine (enteric nerves) and, therefore, mutations in *EDNRB* tend to show pleiotropic effects on pigmentation and enteric nerves. One example is Hirschprung disease II in humans, characterized by an aganglionic megacolon and a white forelock (Amiel et al., 2008). Overo lethal white syndrome is a similar disease in horses caused by a missense mutation Ile118Lys in *EDNRB* (Metallinos et al., 1998; Santschi et al., 1998; Yang et al., 1998). Horses that are heterozygous for this mutation show the Overo white spotting phenotype whereas foals that are homozygous for the mutation are born white and die within days owing to intestinal aganglionosis. Interestingly, white spotting phenotypes caused by *EDNRB2* mutations occur both in Japanese quail (Miwa et al., 2007) and in chicken (Kinoshita et al., 2014), but these are not associated with aganglionosis. The reason for this is that the *EDNRB* gene is duplicated in the avian lineage which has allowed subfunctionalization of the two copies and consequently mutations in *EDNRB2* apparently only affect pigmentation in birds.

Reduced EDNRB signaling is associated with defective melanocyte migration and white spotting phenotypes (lack of pigment cells in skin, hair or feather follicles). Thus, increased EDNRB signaling is expected to lead to expansion of melanocytes and darker pigmentation. A spectacular example of this is fibromelanosis (dermal hyperpigmentation) in chicken, which is characterized by a massive expansion of pigment cells both in skin and in connective tissue. This phenotype is caused by a complex rearrangement causing a duplication of the *EDN3* gene and upregulated expression of the EDN3 transcript (Dorshorst et al., 2011). This specific mutation causes fibromelanosis in a number of breeds including Chinese Silkie chicken, Ayam Cemani from Indonesia, Black H'mong from Vietnam and Svarthöna from Sweden (Dorshorst et al., 2011).

Growth, development, body weight, milk production and meat quality

Melanocortin-4 receptor

MC4R is a key component of the hypothalamic leptin–melanocortin pathway controlling appetite. This pathway has many components including leptin, the leptin receptor, MSH, agouti-related protein and MC4R (Fatima et al., 2022). In fed individuals, leptin is released from adipose tissue and binds the leptin receptor in the hypothalamus, which in turn stimulates POMC neurons to release MSH which binds MC4R and this MC4R signaling results in a satiety signal and reduced appetite (Kuhnen et al., 2019). Furthermore, expression of agouti-related protein can block MC4R signaling in the same way that ASIP can block MC1R signaling in pigment cells. Mutations in a number of the genes taking part in this pathway cause defects in appetite regulation and mutations, leading to reduced MC4R signaling, which ise associated with hyperphagia and obesity. In humans, more than 160 partial or complete loss-of-function mutations associated with obesity have been reported (Heyder et al., 2019).

There has been strong selection for growth in domestic animals and a good appetite is an essential prerequisite for rapid growth. Therefore, it is unsurprising that *MC4R* is considered a candidate gene for growth and production traits in domestic animals. Kim et al. (2000) reported a significant association between a missense mutation Asp298Asn in *MC4R* and variation in fatness, growth and feed intake in pigs. This association has been supported in several subsequent studies (Bruun et al., 2006; Ovilo et al., 2006). A possible association between *MC4R* and growth has also been suggested for chicken (Kubota et al., 2019), but this result needs to be confirmed by additional studies.

Sequencing of candidate genes for obesity in Labrador Retrievers and Flat-coated Retrievers identified a 14 base pair deletion at nucleotide position 17 in *POMC* (Dittmann et al., 2024; Raffan et al., 2016). The deletion disrupts β-MSH and β-endorphin production and is associated with obesity, higher blood pressure and greater food motivation in these breeds (with an allele frequency of 12% in Labradors and 60% in Flat-coated Retrievers), potentially also influencing other behavioral traits.

Melanocortin-3 receptor

Melanocortin-3 receptor (MC3R) was reported to be a candidate locus for several production traits in chicken such as feed conversion and body weight in commercial broiler breeding stock (Sharma et al., 2008). It was further demonstrated that three missense mutations in chicken were all significantly associated with production traits, but only Gly104Ser and Leu151Arg were linked to severe defects in receptor pharmacology (Zhang et al., 2021). Notably, the MC3R was recently reported to connect energy homeostasis with anxiety-related behavior in mice (Cho et al., 2023), which highlights this receptor as having pleiotropic effects.

G protein-coupled receptor 126

In a study that used whole-genome sequencing to explore the genetic relationships between Berkshire pigs and breeds that are distributed worldwide, the adhesion G protein-coupled receptor 126 (GPR126) (*ADGRG6*) was identified as a genetic component under selection (Li et al., 2014). In principle GPR126 can be activated by mechanical stimuli (Mitgau et al., 2022; Musa et al., 2019) or other external stimuli (Li et al., 2024), as shown by *in vitro* studies, and is involved in the regulation of many physiological parameters (Li et al., 2024), e.g. body length and bone mass (Sun et al., 2020), placental development (Torregrosa-Carrion et al., 2021), 'Schwann cell' function (Fernandez et al., 2017) and glial cell development (Mehta & Piao, 2017), as well as myelination of peripheral nerves (Ravenscroft et al., 2015). In conclusion, GPR126 is of importance for many physiological processes; however, its specific role for genetic change in Berkshire pigs has not yet been clarified (Li et al., 2014).

Serotonin receptors 3C and 3B (HTR3C, HTR1B)

The agonistic ligand serotonin is a neurotransmitter essential for the regulation of milk synthesis in the epithelium of the mammary gland (Fricke & Hernandez, 2023). Genetic polymorphisms in both *HTR1B* and *HTR3C* are reported to be associated with milk yield in cattle (Korkuc et al., 2023; Zhang et al., 2008).

Relaxin family peptide receptor 2 (*RXFP2*, formerly *LGR8*)

Horns, for example, in cattle, goats, yaks and sheep, play a role in social behavior and in defense against predators. Generally, the development of horns involves hundreds of genes and occurs early during embryogenesis, and there is a wide variety of naturally occurring forms of horn size, shape and position, including rare forms of hornlessness (polledness) (Pan et al., 2018; Simon et al., 2022). Horned domesticated animals pose a danger when interacting with humans, which leads to a preference for polled animals and an interest in genetically polled animals (Simon et al., 2022). Of note, genetic causes of polledness are different between the respective species (reviewed in Simon et al., 2022).

Several genes associated with horn size and shape were identified in Tibetan sheep, which includes the GPCR, *RXFP2* (Hu et al., 2019). In addition, a study on Chinese sheep (Pan et al., 2018) detected signals of rapid evolution (a unique haplotype at the *RXFP2* locus under positive selection) of the horn-related *RXFP2* gene in semiferal Tibetan sheep populations and proposed that semi-feralization (feralization='reversed domestication' in which formerly domesticated animals escape controlled breeding or cultivation, e.g. dingos; Gering et al., 2019) is a factor responsible for the large and spiral horn phenotype. Further evidence of the importance of the RXFP2 for horn growth and development (length and shape) was provided by studies on cattle, goats and sheep (Johnston et al., 2013; Simon et al., 2022; Wiedemar et al., 2014; Wiedemar & Drogemuller, 2015).

Specific hormone ligands of GPCRs involved in growth regulation

Several neuroendocrine hormones with impact on animal growth, such as growth hormone, growth-hormone-releasing hormone and somastation, were suggested to be related to domestication (McMahon et al., 2001). Growth-hormone-releasing hormone and somastation are both ligands of GPCRs (somastatin receptors and growth hormone releasing hormone receptor, respectively), which consequently makes these receptors relevant to the genetics of domestication, while these have not been identified yet as direct genetic switches. Interestingly, transgenic growth hormone (Du et al., 1992) of Atlantic salmon has a strong impact on the growth rate in aquaculture systems. This indicates the possibility of a potential animal modification using a modified ligand–GPCR axis, especially given recent developments of new specific peptidic GPCR ligands (Moran et al., 2016), as e.g. dual and triple agonists for diverse class B GPCRs that are highly relevant in weight regulation (Bass et al., 2023; Muller & Tschop, 2022) or superagonistic glycoprotein hormone analogs such as thyrotropin (TSH) and follitropin (Grossmann et al., 1998; Szkudlinski, 2015). Finally, high expression of POMC, the precursor of MCR ligands like MSH and ACTH, might contribute to the special feeding habits of mandarin fish (Lu et al., 2023).

GPCRS AND LIGANDS INVOLVED IN CIRCADIAN RHYTHMS, REPRODUCTION, TASTE AND SMELL

Chronobiological mechanisms are, in addition to other factors, regulated by light (day-length, wavelength constitution) and a diverse set of proteins transmitting a light-induced signal into physiological reactions, like sleeping rhythms, reproduction and regulation of metabolism. The underlying and also species-specific mechanisms of such regulation are under intensive investigation for different branches of the animal kingdom, e.g. in vertebrates including birds, fishes and mammals (Ikegami & Yoshimura, 2013, 2016). These mechanisms have a strong impact on animal traits which is also interesting for domestication, because 'uncoupling' breeds from natural chronobiology can be advantageous in terms of, for example, reproduction (e.g. fertility rhythms) to allow domestic animals to reproduce all year round, or for instance to produce eggs throughout the year.

GPCR hormone ligand thyrotropin

One key protein in chronobiology is the heterodimeric thyrotropin (thyroid stimulating hormone; Nakayama &

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Yoshimura, 2018), a member of the glycoprotein hormone group, that is mainly synthesized by the thyrotrophs of the anterior pituitary gland (Hearn & Gomme, 2000; Szkudlinski et al., 2002) and regulates growth and function of the thyroid gland (Vassart & Dumont, 1992). Thyrotropin α- and β-subunit expression has been reported for specific pituitary cells (ovine, pars tuberalis, PT) (Bockmann, Bockers, et al., 1997), which is interesting with respect to two aspects recognized in previous investigations related to mechanisms of chronobiology and domestication. First, it was demonstrated that transcription and translation of TSH subunits in Djungarian hamsters (*Phodopus sungorus*) are regulated by photoperiod in PT-specific cells (Bockmann et al., 1996). This connection between TSH and photoperiodic regulations was then extended by studies indicating that the TSH-expressing cells of the PT play an ancestral role in seasonal reproductive control among vertebrates (e.g. in the European hamster, *Cricetus crietus*; Hanon et al., 2010), and in mammals this relation provides the missing link between the pineal melatonin signal and thyroid-dependent seasonal biology (Hanon et al., 2008). The involvement of TSH in photoperiodic signal transduction at least for *TSHB*, for which functional action of the expressed single monomeric β-TSH subunit on TSHR can be disclosed (reviewed in Kleinau et al., 2013), was also demonstrated in mice (Ono et al., 2008). Increased TSH expression in the PT of quail (*Callipepla*) was supposed to trigger long-day photoinduced seasonal breeding (Nakao et al., 2008).

TSH receptor

Second, TSHR, which is usually mainly expressed in the follicular epithelial cells of the thyroid gland, is known to also be expressed in extra-thyroidal tissues, including the skin, testis, kidney and eye (Bodo et al., 2010; Cianfarani et al., 2010; de Lloyd et al., 2010; Fernando et al., 2012; Marcus et al., 1988; Rocha et al., 2007), and in the brain (Bockmann, Winter, et al., 1997; Unfried et al., 2009). Moreover, it has been shown that TSHR gene variants have a major impact on light-regulated, seasonal reproduction in the Atlantic herring (*Clupea harengus*) (Chen et al., 2021; Lamichhaney et al., 2017). Interestingly, TSHR is the responsive signaling protein of TSH, and was also identified as a hot-spot of genetic adaptions in domesticated animals, which are more or less uncoupled from natural chronobiology (Karlsson et al., 2016). Whole genome sequencing first revealed that the *TSHR* locus is one of the regions in the genome that shows the strongest genetic differentiation between wild Red Jungle Fowl and domestic chickens (Rubin et al., 2010). Furthermore, in line with findings in chickens, a selective sweep signal at the *TSHR* locus has also been reported in domestic sheep (Kijas et al., 2012). In goats, a TSHR variant (Lys139Arg) was suggested to be associated with changes in the seasonality of reproduction (Signer-Hasler et al., 2022).

GPR176

A genetic study of native Korean cattle identified a selective sweep signal at the GPR176 gene (Lee et al., 2013), but the physiological function of this orphan receptor was unclear at the time of the report. Afterwards it was recognized, that *Gpr176* sets the pace of circadian behavior (Doi et al., 2016). Gpr176 is expressed in a circadian manner by nucleus suprachiasmaticus neurons and represses cAMP signaling in an agonist-independent manner and by activation of the G-protein subclass Gz.

Taste 2 receptors

Characterization of the porcine nutrient and taste receptor gene repertoire in domestic and wild populations across the globe revealed that bitter taste taste 2 receptor (Tas2r family) is a plastic trait, possibly associated with the ability of pigs to adapt to diverse environments, that may be subject to balancing selection (da Silva et al., 2014). Tas2r5 was also reported to be associated with selection in the feralization process of dingos (Zhang et al., 2020).

FINAL REMARKS

In conclusion, there is a wealth of research clearly showing that various GPCRs and diverse GPCR ligands have been associated with animal domestication, and they appear to be involved in core features such as behavior, meat and milk production, and coat/feather color. However, for several identified genes or gene variants further research is needed to clarify the exact molecular role in domestication. Gaining knowledge of the key players at each biological level of domestication may not only be of scientific benefit but may also guide transgenic approaches (genome editing), which could be also relevant under particular circumstances, e.g. changing environmental conditions (Ruan et al., 2017). While the rapid and targeted modification of animals can bring benefits in the production of resources for human needs, there are certainly strong ethical issues and concerns that need to be carefully considered.

AUTHOR CONTRIBUTIONS

Gunnar Kleinau: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; visualization; writing – original draft; writing – review and editing. **Bice Chini:** Conceptualization; data curation; formal analysis; investigation; validation;

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writing – original draft; writing – review and editing. **Leif Andersson:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; supervision; validation; writing – original draft; writing – review and editing. **Patrick Scheerer:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; visualization; writing – original draft; writing – review and editing.

ACKNOWLEDGEMENTS

G.K. and P.S. are supported by grants from the Deutsche Forschungsgemeinschaft through SFB1423 'Structural Dynamics of GPCR Activation and Signaling', project number 421152132, subprojects A01 and A05; through SFB1078 'Protonation Dynamics in Protein Function', project number 221545957, subproject B06; through DFG under Germany's Excellence Strategy – EXC 311 2008/1 (UniSysCat) – 390540038 (Research Unit C/D/E); and through the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska–Curie grant agreement no. 956314 [ALLODD]. L.A. is supported by Vetenskapsrådet (2017-02907) and the Knut and Alice Wallenberg Foundation (KAW 2016.0361). B.C. is supported by National Recovery and Resilience Plan funded by the European Union, NextGenerationEU Project PRIN2022JLA3EA by the Italian Ministry of University and Research (MUR). Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Kleinau, G., Chini, B., Andersson, L. & Scheerer, P. (2024) The role of G protein-coupled receptors and their ligands in animal domestication. *Animal Genetics*, 00, 1–14. Available from: https://doi.org/10.1111/age.13476

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