e-ISSN 1734-9168
http://www.isez.pan.krakow.pl/en/folia-biologica.html

Folia Biologica (Kraków), vol. 69 (2021), No3
https://doi.org/10.3409/fb_69-3.14

# Functioning of the Proopiomelanocortin (POMC) Derived Hormones: Melanocyte Stimulating Hormones and Adrenocorticotropic Hormone in Birds

Colin G. SCANES and Krystyna PIERZCHAŁA-KOZIEC

*Accepted September 21, 2021* *Published online September 30, 2021* *Issue online October 13, 2021*

Review article

SCANES C.G., PIERZCHAŁA-KOZIEC K. 2021. Functioning of the proopiomelanocortin (POMC) derived hormones: melanocyte stimulating hormones and adrenocorticotropic hormone in birds. Folia Biologica (Kraków) **69**: 121-134.

In birds, proopiomelanocortin (POMC) is processed to the following biologically active peptides: adrenocortical hormone (ACTH), β-endorphin, α-melanocyte stimulating hormone (MSH), β-MSH, γ-MSH ($\gamma_1$-MSH, $\gamma_2$-MSH and $\gamma_3$-MSH). While ACTH, α-MSH and β-endorphin are present in all birds, β-MSH, γ1-MSH, γ2-MSH and γ3-MSH are present in most but not all avian species. Moreover, there is close homology between the structures across aves. This argues for importance of these peptides in birds. With the exception of β-endorphin, these peptides bind to melanocortin receptors (MCR) with five such receptors identified in one avian species, namely, MC1R, MC2R, MC3R, MC4R and MC5R. There are multiple questions on the POMC peptides and their receptors that warrant investigation in birds, particularly what are the physiological significance of the multiple forms of MSH?

Key words: Aves, ACTH, MSH, hormones expression.

*Colin G. SCANES, Center of Excellence in Poultry Science, University of Arkansas, Fayetteville, AR, United States of America; Department of Biological Sciences, University of Wisconsin Milwaukee, Milwaukee, WI, United States of America.*
*Krystyna PIERZCHAŁA-KOZIEC✉, Department of Animal Physiology and Endocrinology, University of Agriculture, Al.Mickiewicza 24/28, 30-059 Kraków, Poland.*
*E-mail: rzkoziec@cyf-kr.edu.pl*

Proopiomelanocortin (POMC) is a glycoprotein that contains multiple cryptic biologically active peptides namely the following: adrenocortical hormone (ACTH), β-endorphin, α-melanocyte stimulating hormone (MSH), β-MSH and γ-MSH. The POMC is present in across the vertebrates (e.g. lampreys: TAKAHASHI *et al*. 1995; DORES *et al*. 2014) together with invertebrates (e.g. OTTAVIANI *et al*. 1995). It was concluded that POMC was present prior to the split of protostomian and deuterostomian lineages (MALAGOLI *et al*. 2011). The present communication addresses POMC in birds.

Cleavage of double basic (KK, RR, KR or RK) amino-acid residue couplets in POMC by prohormone convertases (PC) 1/3 and 2 generates these peptides (reviewed e.g. DORES *et al*. 2016; LOWRY 2016) (for schematic representation of this – see Fig. 1A). POMC is considered as highly conserved across the vertebrates (DORES *et al*. 2016). With the exception of β-endorphin, the POMC peptides act by binding to melanocortin receptors (MCR). The questions addressed are whether these systems apply to POMC in birds.

## Evolutionary and Structural Aspects of POMC

The sequences of POMC has been deduced for multiple avian species (see Fig. 5 for partial list). Based on the presence of double basic amino-acid couplets, the processing and resultant peptides can be discerned. In birds, POMC can be processed following the conventional model (Figure 1 model A) but also in some species by either of two other schemes (Fig. 1 models B and C). All avian POMC reported contain at least two cryptic peptides, β-endorphin and ACTH; the latter containing the amino-acid residue sequence for α-MSH (NAUDE *et al*. 2006; TAKAHASHI and MIZUSAWA 2013). In addition, there may be β-MSH, $\gamma_3$-MSH, $\gamma_2$-MSH and $\gamma_1$-MSH (for schemas for processing of $\gamma_3$-MSH – see Fig. 2).

© Institute of Systematics and Evolution of Animals, PAS, Kraków, 2021
Open Access article distributed under the terms of the Creative Commons Attribution License (CC-BY)
http://creativecommons.org/licences/by/4.0
OPEN ACCESS

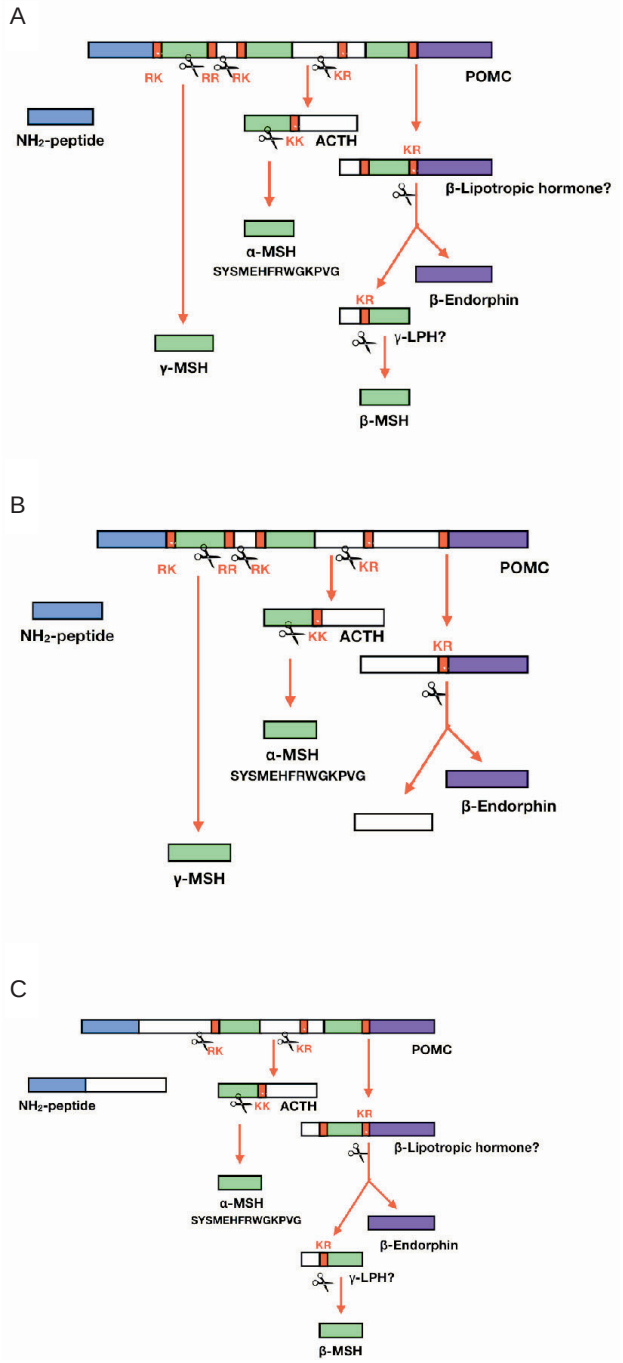


Fig. 1. Conceptual view of the processing of proopiomelanocortin (POMC) in birds to adrenocorticotropic hormone (ACTH) and melanocyte stimulating hormone (MSH). Green – MSH, red – basic amino-acid residue couplet – cleavage site for PC, purple – β-endorphin, blue – N terminal peptide, K – lysine, R – arginine residues. Model A. POMC is processed to generate the following: ACTH, a putative hormone, β-lipotropic hormone (LPH) and γ-MSH. β-LPH is further processed to β-MSH and β-endorphin. ACTH is further processed to α-MSH. Note α-MSH is acetylated (N terminal) and amidated (C terminal). Model B. POMC is processed to generate the following: ACTH, a precursor to β-endorphin and γ-MSH. The precursor to β-endorphin is cleaved to generate β-endorphin. ACTH is further processed to α-MSH. Note α-MSH is acetylated (N terminal) and amidated (C terminal). K – lysine, R – arginine residues. Model C. POMC is processed to generate the following: 1. ACTH and 2. a putative hormone, β-lipotropic hormone (LPH). β-LPH is further processed to β-MSH and β-endorphin. ACTH is further processed to α-MSH. Note α-MSH is acetylated (N terminal) and amidated (C terminal). K – lysine, R – arginine residues.

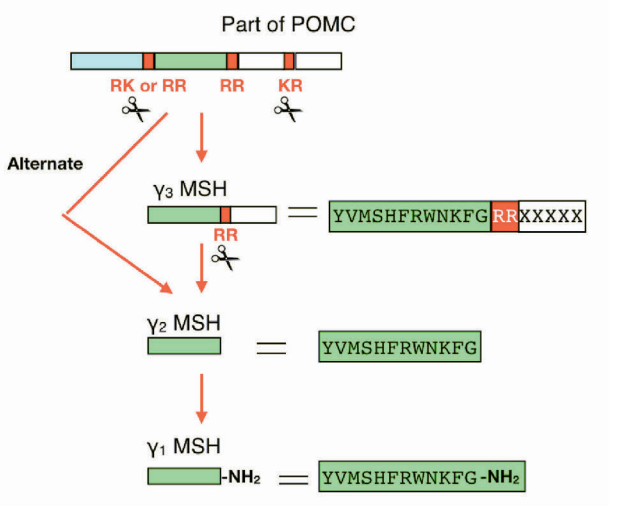


Fig. 2. Processing of avian pro-opiomelanocortin to $\gamma_3$-MSH, $\gamma_2$-MSH and $\gamma_1$-MSH. Green – γ-MSH, R-arginine amino-acid residues, K – lysine amino-acid residues, RK or RR or KR – basic amino-acid residue couplet – cleavage site for PC, blue – N terminal peptide, X – unspecified amino-acid residues, F – phenylalanine, G – glycine, H – histidine, M – methionine, N – asparagine, NH2 – amide, R – arginine, V – valine, W – tryptophan, Y – tyrosine.

## α-MSH

α-MSH is found in all birds examined (Table 1). The structure of α-MSH, a 14 amino-acid residue containing peptide, is identical across the archosaurs (birds and crocodilians) (Fig. 3). These are likely indicative of its importance of α-MSH to the physiology of archosaurs. Moreover, it is assumed to reflect the rigid requirements for effective binding of α-MSH to MCRs.

## β-MSH

Avian β-MSH is an 18 amino-acid residue peptide. It is found in representatives of multiple avian taxa together with the other archosaurs, the Crocodilia (Table 1; Fig. 3). The structure of β-MSH exhibits differences between the crocodilians and birds (Table 1; Fig. 3). However, the requisite with double basic amino-acids residues are missing in some birds and hence so is β-MSH (Table 1). Following loss of cleavage sites, there will be rapid losses of the integrity of the β-MSH sequence.

The β-MSH sequences do not appear to be present in the chimney swift (order Apodiformes), lesser kestrel (order Falconiformes), kakapo and kea (order Psittaciformes) and all oscine passerine birds (excluding white-ruffed manakin) (Table 1). It is not readily apparent what are the reason(s) for the losses of β-MSH in some but not other avian species. It should be noted that once lost, the MSH sequence will tend to be corrupted and, therefore, not recoverable. In the absence of the requisite double basic amino-acids residues, POMC will be processed as in the schema shown in Figure 1B. There are markedly more differences in amino-acid sequences in archosaur β-MSH than α-MSH (Figs 2, 3).

Table 1
Presence of α-MSH, β-MSH and γ-MSH in Archosaurs (Crocodilia and Aves)

| | α-MSH | β-MSH | γ-MSH | ACTH |
|---|---|---|---|---|
| **CROCODILIA** | | | | |
| Australian water crocodile | ✓ | ✓ | ✓ | ✓ |
| Chinese alligator | ✓ | ✓ | ✓ | ✓ |
| **AVES** | | | | |
| **Paleognathae** | | | | |
| Emu | ✓ | ✓ | ✓ | ✓ |
| Kiwi | ✓ | ✓ | ✓ | ✓ |
| **Neognathae** | | | | |
| **Galloanserae** | | | | |
| **Anseriformes** | | | | |
| Mute swan | ✓ | ✓ | ✓ | ✓ |
| Mallard | ✓ | ✓ | ✓ | ✓ |
| Ruddy duck | ✓ | ✓ | ✓ | ✓ |
| Tufted duck | ✓ | X | ✓ | ✓ |
| **Galliformes** | | | | |
| Chicken | ✓ | ✓ | ✓ | ✓ |
| Japanese quail | ✓ | ✓ | ✓ | ✓ |
| Turkey | ✓ | ✓ | ✓ | ✓ |
| Guinea fowl | ✓ | ✓ | ✓ | ✓ |
| **Neoaves** | | | | |
| **Columbiformes** | | | | |
| Pigeon | ✓ | ✓ | ✓ | ✓ |
| **Mesitornithiformes** | | | | |
| Brown roatelo | ✓ | X | X | ✓ |
| **Caprimulgiformes** | | | | |
| Chuck-will's-widow | ✓ | ✓ | ✓ | ✓ |
| **Apodiformes** | | | | |
| Chimney swift | ✓ | X | ✓ | ✓ |
| **Charadriiformes** | | | | |
| Killdear | ✓ | X | ✓ | ✓ |
| Ruff | ✓ | ✓ | ✓ | ✓ |
| *Water birds* | | | | |
| **Pelecaniformes** | | | | |
| Little egret | ✓ | ✓ | X | ✓ |
| Dalmation pelican | ✓ | ✓ | ✓ | ✓ |
| Crested ibis | ✓ | ✓ | ✓ | ✓ |
| **Sphenisciformes** | | | | |
| Emperor penguin | ✓ | ✓ | X | ✓ |
| *Land birds* | | | | |
| **Accipitriformes** | | | | |
| Golden eagle | ✓ | ✓ | ✓ | ✓ |
| **Strigiformes** | | | | |
| Barn owl | ✓ | ✓ | ✓ | ✓ |
| Burrowing owl | ✓ | ✓ | ✓ | ✓ |
| **Falconiformes** | | | | |
| Lesser kestrel | ✓ | X | ✓ | ✓ |
| **Psittaciformes** | | | | |
| Kakapo | ✓ | X | ✓ | ✓ |
| Kea | ✓ | X | ✓ | ✓ |
| **Passeriformes** | | | | |
| **Acanthisittae** | | | | |
| Rifleman | ✓ | ✓ | ✓ | ✓ |
| **Other Passeriformes** | | | | |
| White-ruffed manakin | ✓ | ✓ | ✓+ | ✓ |
| New Caledonian crow | ✓ | X | ✓ | ✓ |
| Common starling | ✓ | X | ✓ | ✓ |
| Swainson's thrush | ✓ | X | ✓+ | ✓ |
| Common canary | ✓ | X | ✓ | ✓ |
| Eurasian tree sparrow | ✓ | X | ✓O | ✓ |
| Small tree finch | ✓ | X | ✓ | ✓ |
| White-rumped snowfinch | ✓ | X | ✓+ | ✓ |
| Zebra finch | ✓ | X | ✓+ | ✓ |
| Great tit | ✓ | ✓O | ✓O | ✓ |
| Brown-headed Cowbird | ✓ | X | ✓+ | ✓ |

✓ – Cleavage sites and peptide sequence, X – one or both cleavage site missing, O – peptide markedly different without an active site, + elongated peptide.

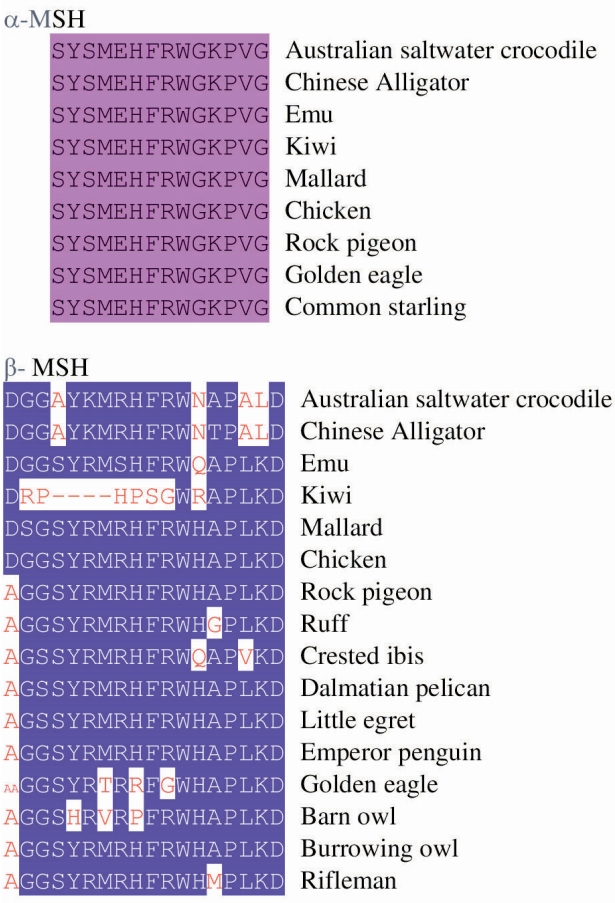


Fig. 3. Examples of the structures of α-MSH, β-MSH in birds with crocodilians for comparison. Red letters indicate difference from ancestral β-MSH (and that in mallards and chickens) (for accession numbers see Figure 5, Table 5), Pink background and black letters – α-MSH, blue background and white lettering – β-MSH

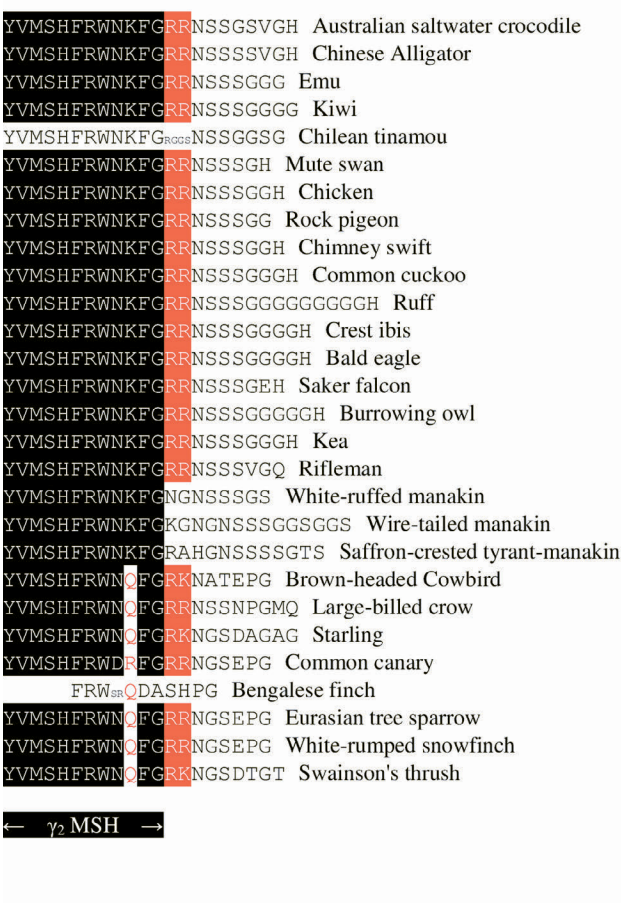


Fig. 4. Structures of avian $\gamma_3$-MSH and γ2-MSH with comparison to crocodilian $\gamma_3$-MSH and $\gamma_2$-MSH. Black background indicates identical structures across aves for $\gamma_2$-MSH, red background indicates cleavable bibasic couplet of amino-acids, red letters indicate difference within $\gamma_2$-MSH (for accession numbers see Figure 5, Table 5).

There are differences between β-MSH in many species of owls with β-MSH having the following sequence AGGSYRMRHFRWHAPLKD but AGGSHRVRPFRWHAPLKD in barn owls (LÖW *et al.* 2020). There are also shifts in the biological activities of β-MSH with MC3R and MC4 (LÖW *et al.* 2020).

## γ-MSH

While the structures of avian γ-MSH have been established in multiple birds (Table 1), there is no information on the potencies of $\gamma_2$-MSH and $\gamma_3$-MSH relative to avian MCRs. $\gamma_3$-MSH is found in representatives of multiple avian taxa together with the other archosaurs, the Crocodilia (Table 1). Figure 4 summarizes the structures of $\gamma_3$-MSH and $\gamma_2$-MSH in birds while Figure 2 shows the three possible schema of processing of POMC to generate $\gamma_3$-MSH and subsequently $\gamma_2$-MSH and then $\gamma_1$-MSH.

While $\gamma_3$-MSH is 18 amino-acid residues peptide in mammals, $\gamma_3$-MSH varies in size in birds and crocodilian from 20 to 28 amino-acid residues (Fig. 4). The C terminal peptide is composed of asparagine at residue 15, a triplet of serine residues followed by a glycine or multiple glycine residues; the number ranging from one to nine (Fig. 4). Across the vast majority of avian and crocodilian species, there are dibasic cleavage sites at residues 13 and 14 (Fig. 4). Cleavage of this site, generates $\gamma_2$-MSH (Fig. 2 and 4). In both mammals and birds, $\gamma_2$-MSH is a 12 amino-acid residue containing peptide while $\gamma_1$-MSH is an 11 amino-acid residue containing peptide (Fig. 4).

The overall $\gamma_3$-MSH sequence and/or the cleavable basic amino-acid residue couplets are present in most avian species; being missing from only a few birds including the brown roatelo, emperor penguin and little egret (Table 1). The sequence for avian $\gamma_2$-MSH are almost identical across avian and crocodilian species (Fig. 3). In some passerine birds, the cleavage site in $\gamma_3$-MSH is not present and, hence, $\gamma_1$-MSH and $\gamma_2$-MSH cannot be generated (Fig. 4). It is unclear whether or not the elongated forms of γ-MSH in some passerine birds have retained the full biological ac-

Table 2

Residues in ACTH that differ in different taxonomic groups within the Archosauromorpha (Crocodilia and Aves)

| Taxonomic Groups | Position | | | |
|---|---|---|---|---|
| | 28 | 35 | 37 | Other |
| **ARCHOSAUROMORPHA** | | | | |
| CROCODILIA | E | Y | L | |
| AVES | | | | |
| Paleognathae | V | F | L | 31-34 |
| Neognathae | | | | |
| Galloanserae | | | | |
| Anseriformes | D | Y | L | – |
| Galliformes | D/E | Y | M/V | – |
| Neoaves | | | | |
| Columbiformes | E | Y | M | – |
| Mesitornithiformes | E | Y | M | – |
| Musophagiformes | E | Y | M | – |
| Cuculiformes | E | Y | L | – |
| Caprimulgiformes | E | Y | L | – |
| Apodiformes | E | Y | L | 21, 23, 30 |
| Opisthocomiformes | E | Y | L | – |
| Pterocliformes | E | Y | L | – |
| Charadriiformes | E | Y | L | 34 |
| *Water birds* | | | | |
| Pelecaniformes | E | Y | L | – |
| Procellariformes | E | Y | L | – |
| Sphenisciformes | E | Y | L | 30 |
| *Land birds* | | | | |
| Bucerotiformes | E | Y | L | 20, 25 |
| Leptosomiformes | E | Y | L | 20 |
| Accipitriformes | E | Y | L | – |
| Strigiformes | E | Y | L | – |
| Falconiformes | E | Y | L | – |
| Psittaciformes | E | Y | L | 31 |
| Passeriformes | | | | – |
| Acanthisittae | E | Y | L | – |
| Other Passeriformes | E/Q | P/Q/R | L/P | 20, 27, 31, 34, 36 plus insertions |

tivities. The conservation of the presence of γ-MSH together with its identical sequence across avian orders supports the importance of γ-MSH in birds. What is unclear is the relative activities of $\gamma_1$-MSH, $\gamma_2$-MSH and $\gamma_3$-MSH in birds.

The increases are in the number of serine repeats in γ-MSH in barn owls (LÖW *et al*. 2020). This has been demonstrated to influence PC cleavage and, thereby, the ratio of $\gamma_3$-MSH to $\gamma_2$-MSH (LÖW *et al*. 2020).

ACTH

The structures of ACTH across avian taxa together with crocodilian are shown in Fig. 5 A,B,C, Table 5. There are few differences in the sequences in Crocodilia and Neognathae except for oscine passerine birds (Table 2). Moreover, the sequences were identical in birds of the following orders: Cuculiformes, Caprimulgiformes, Opisthocomiformes, Pterocliformes, Charadriiformes, Pelecaniformes, Procellariformes, Accipitriformes, Strigiformes, Falconiformes and Sub-order Acanthisitta (order Passeriformes). However, there were multiple differences in the ACTH sequences in oscine passerine birds (Fig. 5, Table 2,5). Avian ACTH increases plasma concentrations of corticosterone (e.g. turkey: SCANES *et al*. 2020).

Ancestral sequences

The ancestral sequences of ACTH, α-MSH, β-MSH and γ-MSH in birds were deduced by comparison of the structures together with the slow rates of evolution in crocodilian and ratites and faster rates of evolution in passerines and chickens (GREEN *et al*. 2014) (Fig. 6). The HFRW motif is found in ACTH, α-MSH, β-MSH and γ-MSH (BARLOCK *et al*. 2014). It is reasonable to conclude that the motif is important to biological activity. In a series of elegant studies with alanine substitutions in human ACTH 1-24, the critical sequences for biological activity have been examined (BARLOCK *et al*. 2014). For instance, substitutions in the $H^6F^7R^8W^9$ and $K^{15}K^{16}R^{17}R^{18}$ motifs resulted in either total inactivity or greater than 100 fold loss of activity (BARLOCK *et al*. 2014).

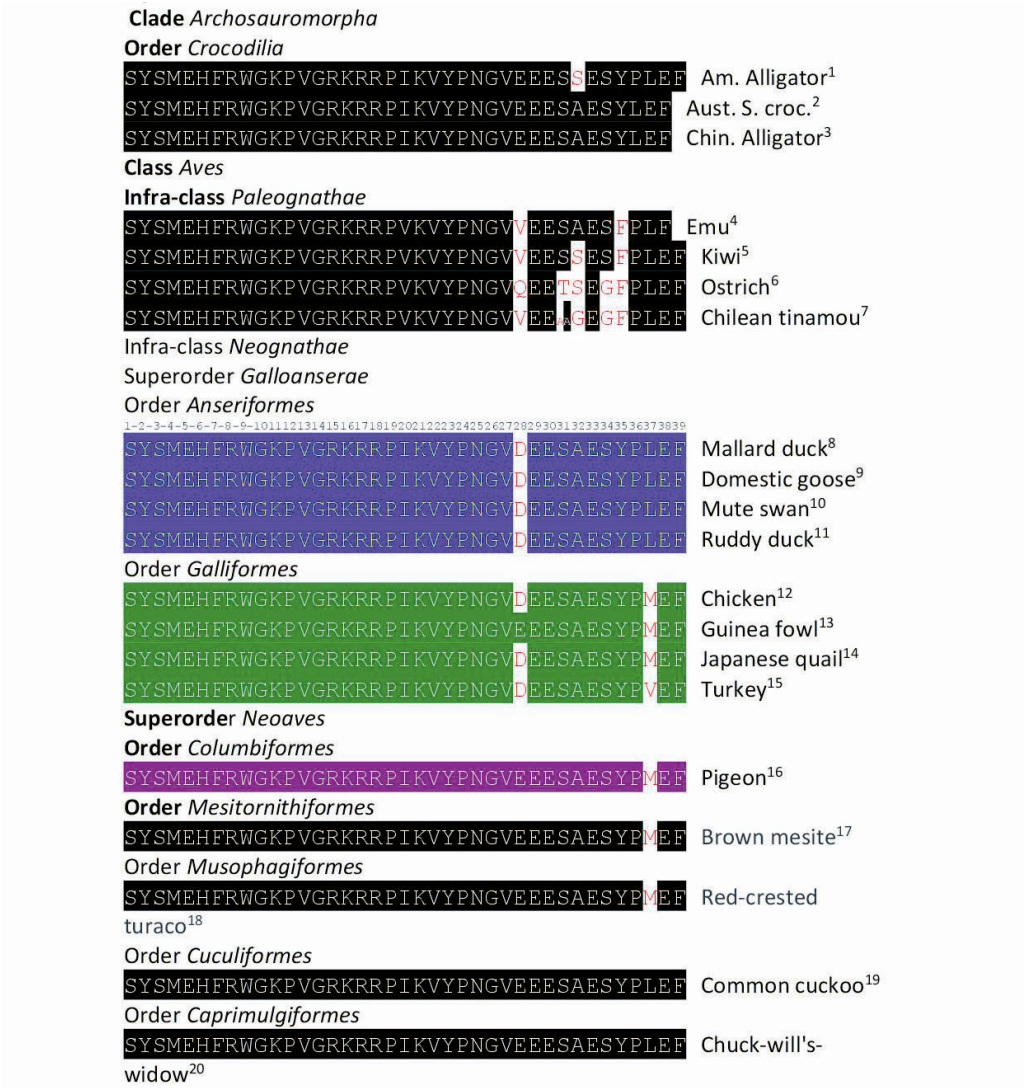


Fig. 5. A. Comparison of the sequence of amino-acid residues in ACTH in Archosaurs including birds and crocodilian. Solid backgrounds indicates identical structures across clade for ACTH, different background colors indicate different clades, red letters indicate difference within ACTH (for numbers see Table 5).

For instance, there would suggest that they have been retained for almost 200 million years from the time of the last common ancestor of birds and crocodilians 240 million years ago (GREEN *et al*. 2014) to at least the divergence of the oscine passerine birds from the suboscines about 43 MYA (e.g. ERICSON *et al*. 2014; OLIVEROS *et al*. 2019) due to its physiological importance. There are incidences where the cleavage sites in POMC, essential to generate β- MSH or γ-MSH, are lost and/or β-MSH and γ-MSH motifs is corrupted or missing.

## Prohormone convertase (PC)

POMC is processed by prohormone convertase (PC) 1/3 to generate ACTH and PC 2 to generate α-MSH, β-MSH and $\gamma_3$-MSH (Figure 1) (LING *et al*. 2004).

There is high expression of PC1 in the pituitary gland, lungs, pancreas, brain, gizzard, spleen, bursa Fabricius, adipose tissue, skeletal and muscle together with moderate to low expression in the heart and kidneys and no expression in the liver of chickens (LING *et al*. 2004). There is high expression of PC2 in the pituitary gland, heart, lungs, gizzard, pancreas, spleen, bursa Fabricius, kidneys, adipose tissue, skeletal muscle, liver and brain of chickens (LING *et al*. 2004).

## Expression of POMC

While there is high expression of POMC in the pituitary gland, there is also POMC expression in other organs including the heart, lungs, gizzard, pancreas, spleen, bursa Fabricius, kidneys, adipose tissue, skeletal muscle and brain of chickens (LING *et al*. 2004). Moreover, POMC expression was not detected in the liver (LING *et al*. 2004).


Fig. 5. B. Comparison of the sequence of amino-acid residues in ACTH in Archosaurs including birds and crocodilian. Solid backgrounds indicates identical structures across clade for ACTH, different background colors indicate different clades, red letters indicate difference within ACTH (for numbers see Table 5).

There are shifts in POMC expression with physiological status in birds. For instance, incubating chickens exhibit marked decreases in feed consumption but no changes in POMC expression. If the comparison is made between incubating hens and pair fed birds, there is greater hypothalamic expression of POMC in incubating hens (DUNN *et al*. 2015).

## Melanocortin Receptors

MCR are members of the superfamily of seven--transmembrane domain containing G-protein-coupled receptors with intra- and extra- cellular loops. There is marked synteny for the receptors for most of the peptides generated from POMC except β-endorphin (SCHIÖTH *et al*. 2003).

MSH acts *via* the following melanocortin receptors (MCR): MC1R to increase eumelanin synthesis in melanocytes and hence feather color (TAKEUCHI *et al*. 1996) and *via* MC4R to modulate feed intake (TAKEUCHI and TAKAHASHI 1999). It is suggested that MSH acts *via* MC3R controlling energy homeostasis and *via* MC5R to influence exocrine gland physiology (TAKEUCHI and TAKAHASHI 1999). Moreover, ACTH acts *via* MC2R, and possibly MC3R, to stimulate adrenal production of glucocorticoid (TAKEUCHI and TAKAHASHI 1998; TAKEUCHI *et al*. 1998; reviewed e.g. DORES *et al*. 2014).

In birds, there are five sub-types of the melanocortin receptor (MCR); respectively, MC1R, MC2R, MC3R, MC4R and MC5R. The structures of MCRs have been deduced from cDNA initially in chickens: MC1R

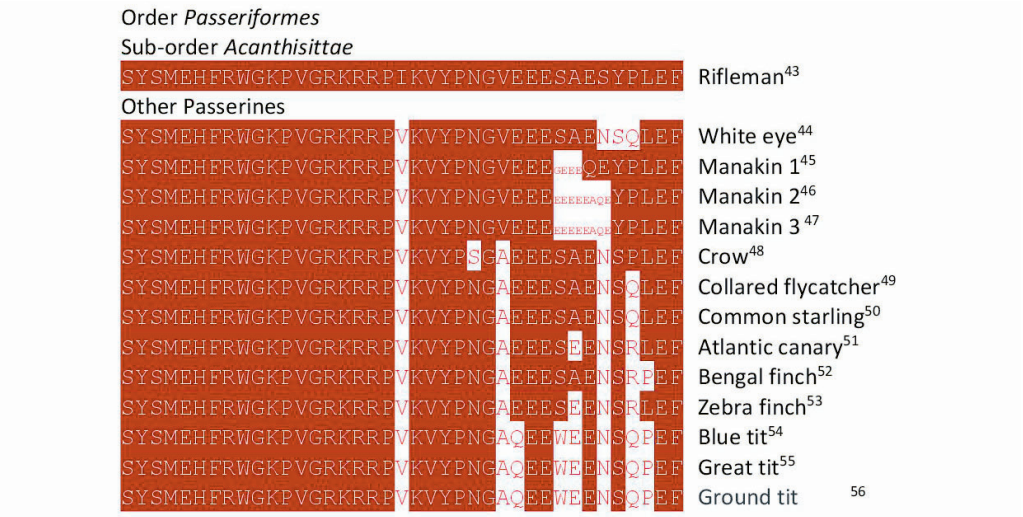


Fig. 5. C. Comparison of the sequence of amino-acid residues in ACTH in Archosaurs including birds and crocodilian. Solid background indicates identical structures across clade for ACTH, different background colors indicate different clades, red letters indicate difference within ACTH (for numbers see Table 5).

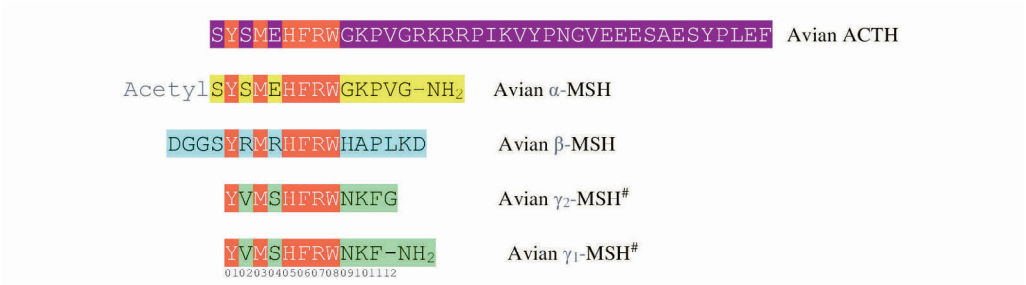


Fig. 6. Ancestral structures of α-MSH (yellow background), β-MSH (blue background), γ- MSH (green background) and ACTH (purple background) in birds. Red backgrounds indicate common amino-acid residues with HFRW common in α-MSH, β- MSH and γ-MSH and essentia.

(TAKEUCHI *et al*. 1996), MC2R (TAKEUCHI *et al*. 1998), MC3R (TAKEUCHI and TAKAHASHI 1999), MC4R and MC5R (TAKEUCHI and TAKAHASHI 1998). In addition, these structures of MCRs have been reported in multiple birds e.g. MC2R in the Mariana crow (*Corvus kubaryi*) (NCBI Reference Sequence: XM_042032180.1), zebra finch (*Taeniopygia guttata*) (NCBI Reference Sequence: XM_002190248.4), golden eagle (*Aquila chrysaetos*) (NCBI Reference Sequence: XM_030012110.1) and MC3R in Mariana crow (*Corvus kubaryi*) (NCBI Reference Sequence: XM_042045276.1).

The different chicken MCRs exhibit the ability to discriminate between α-MSH, β-MSH, γ-MSH and ACTH with the potencies based on Table 3 (LING *et al*. 2004; ZHANG *et al*. 2017) being the following:

MC1R: α-MSH = β-MSH > ACTH = $\gamma_1$-MSH

MC2R: ACTH >>> α-MSH = β-MSH = γ1-MSH

MC3R: $\gamma_1$-MSH > α-MSH = ACTH > β-MSH

MC4R: α-MSH = β-MSH > ACTH >> $\gamma_1$-MSH

MC5R: α-MSH = β-MSH > ACTH $\gamma_1$-MSH.

Table 3

Comparison of the potencies ($K_i$ as nmol/l)$^{\Delta}$ of MSH and ACTH for chicken MCRs (data from LING *et al*. 2004)

| | MC1R | MC3R | MC4R | MC5R |
|---|---|---|---|---|
| α-MSH | 363 | 24 | 40.6 | 189 |
| β-MSH | 346 | 151 | 50.2 | 166 |
| $\gamma_1$-MSH | 1039 | 3.4 | 586 | 654 |
| ACTH | 806 | 15.4 | 88 | 107 |

$^{\Delta}$The lower the $K_i$, the greater the potency

For example, ACTH stimulates production of cAMP from M3 cells transfected with chicken MC2R but α-MSH is ineffective (LING *et al*. 2004). There is evidence that $\gamma_2$-MSH and $\gamma_1$-MSH exert opposite effects in mammals (e.g. JANSONE *et al*. 2004). Unfortunately, there is no evidence for this effect in birds.

The distribution of MCR classes in organs of birds is summarized in Table 4. MC4R is the most widely distributed MCR while MC2R is only found in the adrenal gland.

Table 4

Expression of MCRs together with MRAP1 and 2 in different chicken tissues (based on data in REN *et al*. 2017; THOMAS *et al*. 2018)

| | MC1R | MC2R | MC3R | MC4R | MC5R | MRAP1 | MRAP2 |
|---|---|---|---|---|---|---|---|
| Abdominal adipose tissue | 0 | 0 | 0 | ++++ | + | 0 | 0 |
| Adrenal gland | + | ++ | + | + | +++ | ++++ | + |
| Duodenum | 0 | 0 | 0 | +++ | + | 0 | 0 |
| Gizzard | 0 | 0 | 0 | +++ | 0 | + | 0 |
| Heart | +++ | 0 | 0 | +++ | + | 0 | 0 |
| Hypothalamus | + | 0 | ++ | ++++ | ++ | 0 | +++ |
| Kidneys | ++ | 0 | +++ | +++ | + | 0 | + |
| Liver | +/0 | 0 | +/0 | +/0 | +++ | 0 | ++ |
| Lungs | ++++ | 0 | + | +++ | +++ | + | 0 |
| Ovary | + | 0 | + | + | 0 | 0 | 0 |
| Pancreas | 0 | 0 | + | 0 | 0 | 0 | 0 |
| Pectoralis | + | 0 | 0 | + | 0 | 0 | 0 |
| Spleen | + | 0 | ++ | ++++ | 0 | + | 0 |

**Melanocortin receptor 1 (MC1R)**: Activation of MC1R by binding of MSH is followed by increased synthesis of the black or brown pigment, eumelanin (reviewed MUNDY 2005). Low MC1R activity (both receptor numbers and lack of MSH binding) is thought to generally lead to increased synthesis of red or yellow phaeomelanin (reviewed MUNDY 2005). There is a relationship between mutations/polymorphisms in MC1R and feather coloration (e.g. bananaquit: THERON *et al*. 2001; chicken: KERJE *et al*. 2003; YANG *et al*. 2019; guinea fowl: VIDAL *et al*. 2010; pigeon: GUERNSEY *et al*. 2013; RAN *et al*. 2016; swans: POINTER and MUNDY 2008).

Expression of MR1R is greatest in the melanocytes, lungs and heart (reviewed: MUNDY 2005; REN *et al*. 2017; THOMAS *et al*. 2018) (Table 3). A mutation in MC1R induces it to be constituently active and this is associated with the dominant allele (*E*) in chickens (TAKEUCHI *et al*. 1996). Agouti signaling protein (ASIP), formerly referred to as agouti or agouti protein, acts as an antagonist of MC1R.

**Melanocortin receptor 2 (MC2R)**: ACTH stimulates the synthesis of glucocorticoids by adrenocortical cells. In the presence of melanocortin-2 accessory protein 1, ACTH but not α-MSH, induced CRE – luceriferase activity in a dose dependent manner in CHO cells transfected with both chicken MC2R and cMRAP1 (BARLOCK *et al*. 2014). MC2R appears to be only expressed in the adrenal gland (REN *et al*. 2017; THOMAS *et al*. 2018) (Table 3).

**Melanocortin receptor 3 (MC3R)**: Agouti-related protein/Agouti-related transcript (AGRP/ART) is an endogenous antagonist of the MC3R (TAKEUCHI and TAKAHASHI 1999). Incubating chickens exhibit marked decreases in feed consumption but increases in the medial hypothalamic expression of agouti-related peptide (AgRP) (DUNN *et al*. 2015).

**Melanocortin receptor 4 (MC4R)**: MC4R is predominantly expressed in the brain (reviewed: TAO 2010). As MC3R is not expressed in the brain of birds (TAKEUCHI and TAKAHASHI 1999), it is likely that the central nervous effects of MSH, including modulating feed intake, are mediated by MC4R (reviewed: TAO 2010).

**Melanocortin receptor 5 (MC5R)**: Chicken MRAP1 potentiated the activity of ACTH on the chicken MC5R (DORES *et al*. 2020).

## Melanocortin-receptor accessory proteins (MRAP)

In birds, melanocortin-receptor accessory proteins (MRAP) potentiate the activity of ACTH.

MRAP1 potentiates the ability of ACTH to stimulate CHO cells transfected with chicken MC2R or MC3R or MC4R or MC5R (BARLOCK *et al*. 2014; THOMAS *et al*. 2018). Moreover, in the presence of MRAP 2, there is increased induction CRE – luceriferase activity by ACTH but not α-MSH, in CHO cells transfected with both chicken MC2R and cMRAP1 (BARLOCK *et al*. 2014). Hepatic expression of MRAP1 increases with post-hatch growth/age and estradiol administration (REN *et al*. 2017).

## Circulating concentrations of POMC fragments

There is little information on the circulating concentrations of POMC products in birds. Exceptions to this are the following:

– ACTH in young turkeys 16.4 pg/ml [3.61 pmol/l] (CARSIA and MCILROY 1998)

– α-MSH in chickens 3.1 ng/ml [1.86 nmol/l] (SHIPP *et al*. 2017)

– α-MSH in ptarmigan 0.21-1.83 ng/ml [0.13-1.10 nmol/l] (HÖHN and BRAUN 1980).

Table 5

List of Archosaur ACTHs with structures in Figure 5

| Number | Species | | Accession # or reference |
|---|---|---|---|
| 1 | American alligator | *Alligator mississippiensis* | NM_001287606 |
| 2 | Australian saltwater crocodile | *Crocodylus porosus* | XM_019537236 |
| 3 | Chinese alligator | *Alligator sinensis* | XM_006037658 |
| 4 | Emu | *Dromaius novaehollandiae* | XM_019537236.1 |
| 5 | Okarito kiwi | *Apteryx rowi* | XM_006037658.1 |
| 6 | Ostrich | *Struthio camelus* | NAUDÉ *et al*., 2006 |
| 7 | Chilean tinamou | *Nothoprocta perdicaria* | XM_026041064.1 |
| 8 | Domestic duck/mallard | *Anas platyrhynchos* | XM_013103743.2 |
| 9 | Domestic goose | *Anser cygnoides* | XM_013184389.1 |
| 10 | Mute swan | *Cygnus olor* | XM_040552292 |
| 11 | Ruddy duck | *Oxyura jamaicensis* | XM_035322040.1 |
| 12 | Chicken | *Gallus gallus* | NM_001031098.1 |
| 13 | Helmeted guineafowl | *Numida meleagris* | XM_021391833.1 |
| 14 | Japanese quail | *Coturnix japonica* | AB620013.1 |
| 15 | Turkey | *Meleagris gallopavo* | XM_010708068.2 |
| 16 | Pigeon | *Columba livia* | XM_021298522.1 |
| 17 | Brown mesite | *Mesitornis unicolor* | XM_010179294.1 |
| 18 | Red-crested turaco | *Tauraco erythrolophus* | XM_009985137.1 |
| 19 | Common cuckoo | *Cuculus canorus* | XM_009563761.1 |
| 20 | Chuck-will's-widow | *Caprimulgus carolinensis* | XM_010168282.1 |
| 21 | Anna's hummingbird | *Calypte anna* | XM_010168282.1 |
| 22 | Chimney swift | *Chaetura pelagica* | XM_010168282.1 |
| 23 | Hoazin | *Opisthocomus hoazin* | XM_009942707.1 |
| 24 | Yellow-throated sandgrouse | *Pterocles gutturalis* | XM_010086922.1 |
| 25 | Killdear | *Charadrius vociferous* | XM_009895447.1 |
| 26 | Ruff | *Calidris pugnax* | XM_014937960.1 |
| 27 | Crested ibis | *Nipponia nippon* | XM_009467389.1 |
| 28 | Dalmatian pelican | *Pelecanus crispus* | XM_009480535.1 |
| 29 | Little egret | *Egretta garzetta* | XM_009645266.1 |
| 30 | Northern fulmar | *Fulmarus glacialis* | XM_009583159.1 |
| 31 | Emperor penguin | *Aptenodytes forsteri* | XM_009283455.1 |
| 32 | Rhinoceros hornbill | *Buceros rhinoceros* | XM_010086922.1 |
| 33 | Cuckoo roller | *Leptosomus discolor* | XM_009951222.1 |
| 34 | Golden eagle | *Aquila chrysaetos* | XM_011590841.1 |
| 35 | Bald eagle | *Haliaeetus leucocephalus* | XM_010583178.1 |
| 36 | Burrowing owl | *Athene cunicularia* | XM_026846196.1 |
| 37 | Tawny owl | *Strix aluco* | KF201581.1 |
| 38 | Western barn owl | *Tyto alba* | ID: 116964725 |
| 39 | Saker falcon | *Falco cherrug* | XM_005443524.2 |
| 40 | Peregrine falcon | *Falco peregrinus* | XM_005236654.2 |
| 41 | Kea | *Nestor notabilis* | XM_010014655.1 |
| 42 | Kakapo | *Strigops habroptila* | XM_030491047 |
| 43 | Rifleman | *Acanthisitta chloris* | XM_009069630.1 |
| 44 | Réunion grey white-eye | *Zosterops borbonicus* | XM_027708600.1 |
| 45 | White-ruffed manakin | *Corapipo altera* | XM_027633636.1 |
| 46 | Wire-tailed manakin | *Pipra filicauda* | XM_027750720.1 |
| 47 | Saffron-crested tyrant-manakin | *Neopelma chrysocephalum* | XM_027708600.1 |
| 48 | Large-billed crow | *Corvus macrorhynchos* | AB555653.1 |
| 49 | Collared flycatcher | *Ficedula albicollis* | XM_005062757.1 |
| 50 | Common starling | *Sternus vulgaris* | XM_014893977.1 |
| 51 | Atlantic canary | *Serinus canaria* | XM_009100091.2 |
| 52 | Bengal finch | *Lonchura striata* | XM_021543157.1 |
| 53 | Zebra finch | *Taeniopygia guttata* | XM_002198019.3 |
| 54 | Blue tit | *Cyanistes caeruleus* | M_023946233.1 |
| 55 | Great tit | *Parus major* | XM_015643499.1 |
| 56 | Ground tit | *Pseudopodoces humilis* | XM_005534199.1 |

It is unclear whether circulating concentrations of α-MSH are in fact almost three orders of magnitude greater than those for ACTH or is this an artifact of there being limited available studies. What is also unclear is whether the few studies reflect accurate, precise and specific determinants of α-MSH and ACTH. What is needed is to determine α-MSH, and ACTH in different physiological states and multiple avian species.

## MSH and feed intake

There is close similarity between the roles of melanocortin neuropeptides in the control of feeding (BOSWELL and DUNN 2015; CAO *et al*. 2020). There is growing evidence that MSH exerts an intrahypothalamic role inhibiting feed intake in birds (reviewed: SANEYASU *et al*. 2011; BUZALA and JANICKI 2016). This is likely to be due to α-MSH but roles for β-MSH and γ-MSH cannot be precluded. Central administration of α-MSH depressed feed intake in young chickens (SANEYASU *et al*. 2011; HONDA *et al*. 2012) and Japanese quail (LEAR *et al*. 2017). The effect of α-MSH is thought to be mediated *via* the melanocortin 4 receptor in view of the ability of melanocortin 4 receptor antagonists to block its effect (SANEYASU *et al*. 2011). Similarly, intracerebroventricular administration of β-MSH depressed food intake in chicks (KAMISOYAMA *et al*. 2009; SMITH *et al*. 2008); being effective in layer type chicks but not in broiler chicks (HONDA *et al*. 2012) and being ineffective in other studies (SANEYASU *et al*. 2011). In contrast, γ-MSH was effective in one study (SMITH *et al*. 2009) but not in other studies (HONDA *et al*. 2012). Both SHU9119 (general MCR antagonist) and MCL0020 (MC3R/MC4R antagonist) prevented the decrease in feed intake but not the increase in water intake following ICV administration of serotonin in broiler chickens (ZENDEHDEL *et al*. 2012). Intracerebroventricularly administration of α-MSH to chicks that had been fasted for 3 hours, increased expression of neuropeptide Y (NPY), oxytocin receptor and agouti-related peptide mRNAs in the arcuate nucleus but decreased expression of NPY receptor sub-type 1 in the paraventricular nucleus (DELP *et al*. 2017).

## α-MSH and coloration

There are marked coloration in birds (e.g. MUNDY 2018; RASHID *et al*. 2020). Across vertebrates, MSH increases the amount of eumelanin (black/brown pigment) in the skin or skin structures (hair and feathers) acting via the MCR1 (LING *et al*. 2003). This is the case in birds. For instance, increases have been reported in eumelanin-based traits, namely eumelanic flank size and spotted bib, in red-legged partridges (*Alectoris rufa*) after the administration of α-MSH (GALVÁN and ALONSO-ALONSO 2009). Moreover, α-MSH stimulated dark coloration of feathers in ptarmigan (HÖHN and BRAUN 1980), the willow ptarmigan being a species that has seasonal differences in feather coloration with dark feathers in the summer and white feathers in the winter (reviewed: ZINOVA *et al*. 2018). There are concomitant decreases in pheomelanin related traits (GALVÁN and ALONSO-ALONSO 2011). Constituent expression of MCR1 receptors influence feather color (LING *et al*. 2003).

Parenthetically, the proportion of pheomelanic plumage is inversely related to brain size in birds (GALVÁN and ALONSO-ALONSO 2011). Moreover, birds with high pheomelanin have a propensity for cataracts (GALVÁN *et al*. 2012).

## MSH and immune functioning

There is evidence that MSH and MCR are involved in the avian immune system. There is expression of both POMC together with both PC1/3 and PC2 in the bursa Fabricius of the chicken (LING *et al*. 2004). Similarly, not only are POMC together with MC1R, MC4R, and MC5R expressed in the Japanese quail bursa Fabricius but also there are cells containing immune-reactive α-MSH (KOBAYASHI *et al*. 2007; 2009). In addition, α-MSH has been reported to increase primary cell-mediated immune responses of young red-legged partridges *Alectoris rufa* (MOUGEOT *et al*. 2012).

## α-MSH and adipose tissue

There is evidence from *in vivo* and *in vitro* studies that α-MSH influences the adipose tissue of young chickens. *In vivo* administration of α-MSH to four day-old chicks is followed after one hour by increased the expression of CCAAT/enhancer-binding protein β (C/EBPβ) in subcutaneous adipose tissue in a dose dependent manner (SHIPP *et al*. 2017). Moreover, there is increased expression of fatty acid binding protein 4 (FABP4), comparative gene identification - 58 (CGI-58), perilipin-1 (PLIN), melanocortin receptor 5 (MC5R) in stromal-vascular fraction of cells isolated from abdominal fat from 14 day-old broiler chickens treated with α-MSH (SHIPP *et al*. 2017). In addition, *in vitro* α-MSH increased glycerol-3-phosphate dehydrogenase activity in chicken adipose tissue (SHIPP *et al*. 2017). Arguably in an analogous manner, ACTH stimulated *in vitro* lipolysis by chicken adipose tissue (LANGSLOW and HALES 1969). The effects of α-MSH and ACTH are likely to be mediated *via* MC5R. What is unclear is the extent that α-MSH and ACTH interact with other hormones that influence adipose tissue metabolism. Consistent with effects of MSH on adipose tissue, ICV administration of α-MSH depresses the respiratory quotient (TACHIBANA *et al*. 2007).

A role for γ-MSH in the control of hormone sensitive lipase has been proposed (BICKNELL *et al*. 2009). Unfortunately, this has not been examined in birds as yet.

MSH and eye functioning

There is evidence that α-MSH influences the avian eye with MCRs and α-MSH being expressed in cells in the chick retina (TESHIGAWARA *et al*. 2001). Moreover, α-MSH has been demonstrated to reduce glutamate excitotoxicity in the developing chick retina (ZHANG *et al*. 2015).

MSH and pituitary cells

$\gamma_3$-MSH increased intra-cellular calcium concentrations in a sub-population of pituitary cells (DENEF *et al*. 2003). What is not clear is the role of MSH in the control of pituitary hormone secretion.

MSH and other aspects of avian physiology

There is evidence that δ-MSH influences blood pressure, sodium balance and kidney function in mammals (NI *et al*. 2006; CHANDRAMOHAN *et al*. 2009; also see review HUMPHREYS 2004). The presence of an analogous role of δ-MSH in birds has not been examined. Administration of α-MSH *via* intracerebroventricular injection (ICV) did not increase heat production, oxygen consumption or locomotory activity in chicks (TACHIBANA e*et al*. 2007). What is needed is further research into the multiple roles of MSH.

## Author Contributions

Research concept and design: C.G.S; Collection and/or assembly of data: C.G.S; Data analysis and interpretation: C.G.S, K.P.-K.; Writing the article: C.G.S; Critical revision of the article: C.G.S, K.P.-K.; Final approval of article: C.G.S, K.P.-K.

## Conflict of Interest

The authors declare no conflict of interest.

## References


BARLOCK T.K., GEHR D.T., DORES R.M. 2014. Analysis of the pharmacological properties of chicken melanocortin-2 receptor (cMC2R) and chicken melanocortin-2 accessory protein 1 (cMRAP1). Gen Comp Endocrinol. **205**: 260-267. https://doi.org/10.1016/j.ygcen.2014.03.045

BICKNELL K.A., HARMER S.C., YIANGSON S., LOCKWOOD W., BICKNELL A.B. 2009. Lys-gamma3-MSH: A global regulator of hormone sensitive lipase activity? Mol. Cell. Endocrinol. **300**: 71-76. https://doi.org/10.1016/j.mce.2008.09.032

BOSWELL T., DUNN I.C. 2015. Regulation of the avian central melanocortin system and the role of leptin. Gen. Comp. Endocrinol. **221**: 278-283. https://doi.org/10.1016/j.ygcen.2014.12.009

BUZALA M., JANICKI B. 2016. Effects of different growth rates in broiler breeder and layer hens on some productive traits. Poult. Sci. **95**: 2151-2159. https://doi.org/10.3382/ps/pew173

CAO C., GILBERT E.R., CLINE M.A. 2020. The anorexigenic effect of beta-melanocyte-stimulating hormone involves corticotrophin-releasing factor and mesotocin in birds. Neurosci. Lett. **736**: 135282. https://doi.org/10.1016/j.neulet.2020.135282

CARSIA R.V., MCILROY P.J. 1998. Dietary protein restriction stress in the domestic turkey (*Meleagris gallopavo*) induces hypofunction and remodeling of adrenal steroidogenic tissue. Gen. Comp. Endocrinol. **109**: 140-153. https://doi.org/10.1006/gcen.1997.7016

CHANDRAMOHAN G., DURHAM N., SINHA S., NORRIS K., VAZIRI N.D. 2009. Role of gamma melanocyte-stimulating hormone-renal melanocortin 3 receptor system in blood pressure regulation in salt-resistant and salt-sensitive rats. Metabolism **58**: 1424-1429. https://doi.org/10.1016/j.metabol.2009.04.022

DELP M.S., CLINE M.A., GILBERT E.R. 2017. The central effects of alpha-melanocyte stimulating hormone (α-MSH) in chicks involve changes in gene expression of neuropeptide Y and other factors in distinct hypothalamic nuclei. Neurosci. Lett. **651**: 52-56. https://doi.org/10.1016/j.neulet.2017.04.064

DENEF C., LU J., SWINNEN E. 2003. Gamma-MSH peptides in the pituitary: effects, target cells, and receptors. Ann. N.Y. Acad. Sci. **994**: 123-132. https://doi.org/10.1111/j.1749-6632.2003.tb03171.x

DORES R.W., LONDRAVILLE R.L., PROKOP J., DAVIS P., DEWEY N., LESINSKI N. 2014. Molecular evolution of GPCRs: Melanocortin/melanocortin receptors. J. Mol. Endocrinol. **52**: T29-T42. https://doi.org/10.1530/JME-14-0050

DORES R.M., LIANG L., DAVIS P., THOMAS A.L., PETKO B. 2016. 60 years of POMC: Melanocortin receptors: evolution of ligand selectivity for melanocortin peptides. J. Mol. Endocrinol. **56**: T119-T133. https://doi.org/10.1530/JME-15-0292

DORES R.M., OBERER N., HOGLIN B., THOMAS A., FAUGHT E., VIJAYAN M..M. 2020. Evaluating interactions between the melanocortin-5 receptor, MRAP1, and ACTH (1-24): A phylogenetic study. Gen. Comp. Endocrinol. **294**: 113476. https://doi.org/10.1016/j.ygcen.2020.113476

DUNN I.C., WILSON P.W., D'EATH R.B., BOSWELL T. 2015. Hypothalamic agouti-related peptide mRNA is elevated during natural and stress-induced anorexia. J. Neuroendocrinol. **27**: 681-691. https://doi.org/10.1111/jne.12295

ERICSON P.G.P., KLOPFSTEIN S., IRESTEDT M., NGUYEN J.M.T., NYLANDER J.A.A. 2014. Dating the diversification of the major lineages of Passeriformes (Aves). BMC Evol. Biol. **14**: 8. https://doi.org/10.1186/1471-2148-14-8

GALVÁN I., ALONSO-ALONSO C. 2009. The expression of melanin-based plumage is separately modulated by exogenous oxidative stress and a melanocortin. Proc. Biol. Sci. **276**: 3089-3097. https://doi.org/10.1098/rspb.2009.0774

GALVÁN I., ALONSO-ALONSO C. 2011. Brain size and the expression of pheomelanin-based color in birds. J. Evol. Biol. **24**: 999-1006. https://doi.org/10.1111/j.1420-9101.2011.02232.x

GALVÁN I., ERRITZØE J., WAKAMATSU K., MØLLER A.P. 2012. High prevalence of cataracts in birds with pheomelanin-based colouration. Comp. Biochem. Physiol. **A 162**: 259-264. https://doi.org/10.1016/j.cbpa.2012.03.012

GREEN R.E., BRAUN E.L., ARMSTRONG J., EARL D., NGUYEN N., HICKEY G., VANDEWEGE M.W., ST. JOHN J.A., CAPELLA-GUTIÉRREZ S., CASTOE T.A., KERN C., FUJITA M.K., OPAZO J.C., JURKA J., KOJIMA K.K., CABALLERO J., HUBLEY R.M., SMIT A.F., PLATT R.N., LAVOIE C.A., RAMAKODI M.P., FINGER Jr J.W., SUH A., SBERG S.R., MILES L., CHONG A.Y., JARATLERDSIRI W., GONGORA J., MORAN C., IRIARTE A., MCCORMACK J., BURGESS S.C., EDWARDS S.V., LYONS E., WILLIAMS C., BREEN M., HOWARD J.T., GRESHAM C.R., PETERSON D.G., SCHMITZ J., POLLOCK D.D., HAUSSLER D., TRIPLETT E.W., ZHANG G., IRIE N., JARVIS E.D., BROCHU C.A., SCHMIDT C.J., MCCARTHY F.M., FAIRCLOTH B.C., HOFFMANN F.G., GLENN T.C., GABALDÓN T., PATEN B., RAY D.A. 2014. Three crocodilian genomes reveal ancestral patterns of evolution among archosaurs. Science **346**: 1254449. https://doi.org/10.1126/science.1254449

GUERNSEY M.W., RITSCHER L., MILLER M.A., SMITH D.A., SCHÖNEBERG T., SHAPIRO M.D. 2013. A Val85Met mutation in melanocortin-1 receptor is associated with reductions in eumelanic pigmentation and cell surface expression in domestic rock pigeons (*Columba livia*). PLoS ONE **8**: 8. https://doi.org/10.1371/journal.pone.0074475

HÖHN E.O., BRAUN C.E. 1980. Hormonal induction of feather pigmentation in ptarmigan. Auk **97**: 601-607. https://doi.org/10.1093/auk/97.3.601

HONDA K., SANEYASU T., HASEGAWA S., KAMISOYAMA H. 2012. A comparative study of the central effects of melanocortin peptides on food intake in broiler and layer chicks. Peptides **37**: 13-17. https://doi.org/10.1016/j.peptides.2012.06.015

HUMPHREYS M.H. 2004. Gamma-MSH, sodium metabolism, and salt-sensitive hypertension. Am. J. Physiol. **286**: R417-R430. https://doi.org/10.1152/ajpregu.00365.2003

JANSONE B., BERGSTROMB L., SVIRSKISA S., LINDBLOMB J., KLUSAA V., WIKBERG J.E.S. 2004. Opposite effects of g1- and g2-melanocyte stimulating hormone on regulation of the dopaminergic mesolimbic system in rats. Neurosci. Lett. **361**: 68-71. https://doi.org/10.1016/j.neulet.2003.12.006

KAMISOYAMA H., HONDA K., SANEYASU T., SUGAHARA K., HASEGAWA S. 2009 Corticotropin-releasing factor is a downstream mediator of the beta-melanocyte-stimulating hormone-induced anorexigenic pathway in chicks. Neurosci. Lett. **458**: 102-105. https://doi.org/10.1016/j.neulet.2009.04.041

KERJE S., LIND J., SCHÜTZ K., JENSEN P., ANDERSSON L. 2003. Melanocortin 1-receptor (MC1R) mutations are associated with plumage colour in chicken. Anim. Genet. **34**: 241-248. https://doi.org/10.1046/j.1365-2052.2003.00991.x

KOBAYASHI Y., SAKAMOTO T., IGUCHI K., IMAI Y., HOSHINO M., LANCE V.A., KAWAUCHI H., TAKAHASHI A. 2007. cDNA cloning of proopiomelanocortin (POMC) and mass spectrometric identification of POMC-derived peptides from snake and alligator pituitaries Gen. Comp. Endocrinol. **152**: 73-81. https://doi.org/10.1016/j.ygcen.2007.02.026

KOBAYASHI T., TAKASO A., TANAKA S., AMANO M., TAKAHASHI A., IWAMURO S., MACHIDA T. 2009. Demonstration of the proopiomelanocortin signaling system in the primary immune organ of the quail. Ann. N.Y. Acad. Sci. **1163**: 441-443. https://doi.org/10.1111/j.1749-6632.2009.04430.x

LANGSLOW D.R., HALES C.N. 1969. Lipolysis in chicken adipose tissue *in vitro*. J. Endocrinol. **43**: 285-294. https://doi.org/10.1677/joe.0.0430285

LEAR T., LIU L., O'DONNELL M., MCCONN B.R., DENBOW D.M., CLINE M.A., GILBERT E.R. 2017. Alpha-melanocyte stimulating hormone-induced anorexia in Japanese quail (*Coturnix japonica*) likely involves the ventromedial hypothalamus and paraventricular nucleus of the hypothalamus. Gen. Comp. Endocrinol. **252**: 97-102. https://doi.org/10.1016/j.ygcen.2017.08.005

LING M.K., LAGERSTRÖM M.C., FREDRIKSSON R., OKIMOTO R., MUNDY N.I., TAKEUCHI S., SCHIÖTH H.B. 2003. Association of feather colour with constitutively active melanocortin 1 receptors in chicken. Eur J Biochem. **270**: 1441-1449. https://doi.org/10.1046/j.1432-1033.2003.03506.x

LING M.K., HOTTA E., KILIANOVA Z., HAITINA T., RINGHOLM A., JOHANSSON L., GALLO-PAYET N., TAKEUCHI S., SCHIÖTH H.B. 2004. The melanocortin receptor subtypes in chicken have high preference to ACTH-derived peptides. Br. J. Pharmacol. **143**: 626-637. https://doi.org/10.1038/sj.bjp.0705900

LÖW K., DUCREST A.L., SAN-JOSE L.M., SIMON C., UVA V., SEIDAH N.G., PASQUATO A., KUNZ S., ROULIN A. 2020. Molecular evolution of the proopiomelanocortin system in Barn owl species. PLoS One **15**: e0231163. https://doi.org/10.1371/journal.pone.0231163

LOWRY P. 2016. 60 years of POMC: Purification and biological characterisation of melanotrophins and corticotrophins. J. Mol. Endocrinol. **56**: T1-T12. https://doi.org/10.1530/JME-15-0260

MALAGOLI D., ACCORSI A., OTTAVIANI E. 2011. The evolution of pro-opiomelanocortin: looking for the invertebrate fingerprints. Peptides **32**: 2137-2140. https://doi.org/10.1016/j.peptides.2011.09.008

MOUGEOT F., GALVÁN I., ALONSO-ALONSO C. 2012. Contrasted effects of an oxidative challenge and α-melanocyte-stimulating hormone on cellular immune responsiveness: an experiment with red-legged partridges *Alectoris rufa*. Oecologia **169**: 385-294. https://doi.org/10.1007/s00442-011-2220-9

MUNDY N.I. 2005. A window on the genetics of evolution: MC1R and plumage colouration in birds. Proc. Roy. Soc. **B 272**: 1633-1640. https://doi.org/10.1098/rspb.2005.3107

MUNDY N.I. 2018. Colouration Genetics: Pretty Polymorphic Parrots. Curr. Biol. **28**: R113-R114. https://doi.org/10.1016/j.cub.2017.12.045

NAUDÉ R., OELOFSEN W., TAKAHASHI A., AMANO M., KAWAUCHI H. 2006. Molecular cloning and characterization of preproopiomelanocortin (prePOMC) cDNA from the ostrich (*Struthio camelus*). Gen. Comp. Endocrinol. **146**: 310-317. https://doi.org/10.1016/j.ygcen.2005.11.018

NI X.P., BHARGAVA A., PEARCE D., HUMPHREYS M.H. 2006. Modulation by dietary sodium intake of melanocortin 3 receptor mRNA and protein abundance in the rat kidney. Am. J. Physiol. **290**: R560-R567. https://doi.org/10.1152/ajpregu.00279.2005

OLIVEROS C.H., FIELD D.J., KSEPKA D.T., BARKER F.K., ALEIXO A., ANDERSEN M.J., ALSTRÖM P., BENZ B.W., BRAUN E.L., BRAUN M.J., BRAVO G.A., BRUMFIELD R.T., CHESSER R.T., CLARAMUNT S., CRACRAFT J., CUERVO A.M., DERRYBERRY E.P., GLENN T.C., HARVEY M.G., HOSNER P.A., JOSEPH L., KIMBALL R.T., MACK A.L., MISKELLY C.M., PETERSON A.T., ROBBINS M.B., SHELDON F.H., SILVEIRA L.F., SMITH B.T., NOOR D., WHITE N.D., MOYLE R.G., FAIRCLOTH B.C. 2019. Earth history and the passerine superradiation. Proc. Nat. Acad. Sci. **116**: 7916-7925. https://doi.org/10.1073/pnas.1813206116

OTTAVIANI E., CAPRIGLIONE T., FRANCESCHI C. 1995. Invertebrate and vertebrate immune cells express pro-opiomelanocortin (POMC) mRNA. Brain, Behav. Immun. **9**: 1-8. https://doi.org/10.1006/brbi.1995.1001

POINTER M.A., MUNDY N.I. 2008. Testing whether macroevolution follows microevolution: are colour differences among swans (*Cygnus*) attributable to variation at the MC1R locus? BMC Evol. Biol. **8**: 1. https://doi.org/10.1186/1471-2148-8-249

RAN J.-S., YOU X.-Y., JIN J., ZHOU Y.-G., WANG Y., LAN D., REN P., LIU Y.-P. 2016. The relationship between *MC1R* mutation and plumage color variation in pigeons. Biomed. Res. Int. **2016**: 3059756. https://doi.org/10.1155/2016/3059756

RASHID I., HASSAN M.U., NAZIM M., ELSHERIF M., DOU Q., HU D., KAMRAN M., DAI Q., BUTT H. 2020. Structural colouration in the Himalayan monal, hydrophobicity and refractive index modulated sensing. Nanoscale **21**: 409-21419. https://doi.org/10.1039/d0nr06382g

REN J., LI Y., XU N., LI H., LI C., HAN R., WANG Y., LI Z., KANG X., LIU X., TIAN Y. 2017. Association of estradiol on expression of melanocortin receptors and their accessory proteins in the liver of chicken (*Gallus gallus*). Gen. Comp. Endocrinol. **240**: 182-190. https://doi.org/10.1016/j.ygcen.2016.10.012

SANEYASU T., HONDA K., KAMISOYAMA H., NAKAYAMA Y., IKEGAMI K., HASEGAWA S. 2011. Alpha-melanocyte stimulating hormone plays an important role in the regulation of food intake by the central melanocortin system in chicks. Peptides **32**: 996-1000. https://doi.org/10.1016/j.peptides.2011.03.006

SCANES C.G., HURST K., THAXTON Y., ARCHER G.S., JOHNSON A. 2020. Effects of putative stressors and adrenocorticotropic hormone on plasma concentrations of corticosterone in market-weight male turkeys. Poult. Sci. **99**: 1156-1162. https://doi.org/10.1016/j.psj.2019.11.010

SCHIÖTH H.B., RAUDSEPP T., RINGHOLM A., FREDRIKSSON R., TAKEUCHI S., LARHAMMAR D., CHOWDHARY B.P. 2003. Remarkable synteny conservation of melanocortin receptors in chicken, human, and other vertebrates. Genomics **81**: 504-509. https://doi.org/10.1016/s0888-7543(03)00028-4

SHIPP S.L., WANG G., CLINE M.A., GILBERT E.R. 2017. Chick subcutaneous and abdominal adipose tissue depots respond differently in lipolytic and adipogenic activity to α-melanocyte stimulating hormone (α-MSH). Comp. Biochem. Physiol. **A 209**: 56-64. https://doi.org/10.1016/j.cbpa.2017.04.013

SMITH M.L., PRALL B., NANDAR W., CLINE M.A. 2008. Beta-melanocyte-stimulating hormone potently reduces appetite via the hypothalamus in chicks. J. Neuroendocrinol. **20**: 220-226. https://doi.org/10.1111/j.1365-2826.2007.01639.x

SMITH M.L., KOHART N.A., NEWMYER B.A., CLINE M.A. 2009. Gamma(2)-melanocyte stimulating hormone decreases food intake in chicks. Neurosci. Lett. **465**: 210-213. https://doi.org/10.1016/j.neulet.2009.08.021

TACHIBANA T., OIKAWA D., ADACHI N., BOSWELL T., FURUSE M. 2007. Central administration of alpha-melanocyte-stimulating hormone changes lipid metabolism in chicks. Comp. Biochem. Physiol. **A 148**: 408-412. https://doi.org/10.1016/j.cbpa.2007.05.023

TAKAHASHI A., AMEMIYA Y., NOZAKI M., SOWER S.A., JOSS J., GORBMAN A., KAWAUCHI H. 1995. Isolation and characterization of melanotropins from lamprey pituitary glands. Int. J. Pept. Protein Res. **46**: 197-204. https://doi.org/10.1111/j.1399-3011.1995.tb00589.x

TAKAHASHI A., MIZUSAWA K. 2013. Posttranslational modifications of proopiomelanocortin in vertebrates and their biological significance. Front. Endocrinol. (Lausanne) **4**: 143. https://doi.org/10.3389/fendo.2013.00143

TAKEUCHI S., TAKAHASHI S. 1998. Melanocortin receptor genes in the chicken-tissue distributions. Gen. Comp. Endocrinol. **112**: 220-231. https://doi.org/10.1006/gcen.1998.7167

TAKEUCHI S., TAKAHASHI S. 1999. A possible involvement of melanocortin 3 receptor in the regulation of adrenal gland function in the chicken. Biochim. Biophys. Acta **1448**: 512-518. https://doi.org/10.1016/s0167-4889(98)00165-7

TAKEUCHI S., SUZUKI H., HIROSE S., YABUUCHI M., SATO C., YAMAMOTO H., TAKAHASHI S. 1996. A possible involvement of melanocortin 1-receptor in regulating feather color pigmentation in the chicken. Biochim. Biophys. Acta **1306**: 122-126.

TAKEUCHI S., KUDO T., TAKAHASHI S. 1998. Molecular cloning of the chicken melanocortin 2 (ACTH)-receptor gene. Biochim. Biophys. Acta **1403**: 102-108. https://doi.org/10.1016/s0167-4889(98)00022-6

TAO Y.-X. 2010. The melanocortin-4 receptor: physiology, pharmacology, and pathophysiology. Endocr. Rev. **31**: 506-543. https://doi.org/10.1210/er.2009-0037

THERON E., HAWKINS K., BERMINGHAM E., RICKLEFS R.E., MUNDY N.I. 2001. The molecular basis of an avian plumage polymorphism in the wild: a melanocortin-1-receptor point mutation is perfectly associated with the melanic plumage morph of the bananaquit, *Coereba flaveol*a. Curr. Biol. **11**: 550-557. https://doi.org/10.1016/s0960-9822(01)00158-0

TESHIGAWARA K., TAKAHASHI S., BOSWELL T., LI Q., TANAKA S., TAKEUCHI S. 2001. Identification of avian alpha-melanocyte-stimulating hormone in the eye: temporal and spatial regulation of expression in the developing chicken. J. Endocrinol. **168**: 527-537. https://doi.org/10.1677/joe.0.1680527

THOMAS A.L., MAEKAWA F., KAWASHIMA T., SAKAMOTO H., SAKAMOTO T., DAVIS P., DORES R.M. 2018. Analyzing the effects of co-expression of chick (*Gallus gallus*) melanocortin receptors with either chick MRAP1 or MRAP2 in CHO cells on sensitivity to ACTH(1-24) or ACTH(1-13)$NH_2$: Implications for the avian HPA axis and avian melanocortin circuits in the hypothalamus. Gen. Comp. Endocrinol. **256**: 50-56. https://doi.org/10.1016/j.ygcen.2017.09.002

VIDAL O., ARAGUAS R.M., FERNÁNDEZ R., HERAS S., SANZ N., PLA C. 2010. Melanism in guinea fowl (*Numida meleagris*) is associated with a deletion of Phenylalanine-256 in the MC1R gene. Anim. Genet. **41**: 656-658. https://doi.org/10.1111/j.1365-2052.2010.02056.x

YANG C.-W., RAN J.-S., YU C.-L., QIU M.-H., ZHANG Z.-R., DU H.-R., LI Q.-Y., XIONG X., SONG X.-Y., XIA B., HU C.-M., LIU Y.-P., JIANG X.-S. 2019. Polymorphism in *MC1R*, *TYR* and *ASIP* genes in different colored feather chickens. 3 Biotech. **9**: 203. https://doi.org/10.1007/s13205-019-1710-z

ZENDEHDEL M., HAMIDI F., BABAPOUR V., MOKHTARPOURIANI K., FARD R.M. 2012. The effect of melanocortin (Mc3 and Mc4) antagonists on serotonin-induced food and water intake of broiler cockerels. J. Vet. Sci. **13**: 229-234. https://doi.org/10.4142/jvs.2012.13.3.229

ZHANG Y., BO Q., WU W., XU C., YU G., MA S., YANG Q., CAO Y., HAN Q., RU Y., LIU X., WEI H., WANG F.E., ZHANG X., LI X. 2015. α-Melanocyte-stimulating hormone prevents glutamate excitotoxicity in developing chicken retina via MC4R-mediated down-regulation of microRNA-194. Sci. Rep. **5**: 15812. https://doi.org/10.1038/srep15812

ZHANG J., LI X., ZHOU Y., CUI L., LI J., WU C., WAN Y., LI J., WANG Y. 2017. The interaction of MC3R and MC4R with MRAP2, ACTH, α-MSH and AgRP in chickens. J. Endocrinol. **234**: 155-174. https://doi.org/10.1530/JOE-17-0131

ZINOVA M., HACKLÄNDER K., GOOD J.M., MELO-FERREIRA J., AVES P.C., SCOTT L.C. 2018. Functional and underlying mechanisms of seasonal colour moulting in mammals and birds: what keeps them changing in a warming world. Biol. Rev. **93**: 1478-1498. https://doi.org/10.1111/brv.12405