

Symposium organized to commemorate the 100 years anniversary of the birth of Professor Z. Ewy
Dedication – Professor Z. Ewy – a great academic and researcher
Second dedication to Michael Wnuk – scientist, engineer, friend and a native of Cracow
who introduced me to its traditions and caliber

Colin G. Scanes

THE 100TH ANNIVERSARY OF THE BIRTH OF PROFESSOR Z. EWY

It is a particular honor to the part of the symposium/volume organized to celebrate the 100th anniversary of the birth of Professor Z. Ewy.

Professor Ewy was one of the founders of the field of domestic animal endocrinology. His group performed a series of innovative studies demonstrating the key role of arginine vasotocin (AVT) in oviductal functioning in the adult female chicken. They demonstrated that AVT increases the intra-uterine pressure in the hen (RZASA and EWY, 1971). Moreover, AVT was found to be much more potent and effective than oxytocin in eliciting the response (RZASA and EWY, 1971) suggesting marked differences in the receptor. The receptivity of the oviductal muscles was found to be changed by either progesterone or estrogen (RZASA and EWY, 1982). Professor Ewy's group also definitively demonstrated, using bioassay, that there were large increases in circulating concentrations of AVT at the time of oviposition (NIEZGODA et al., 1973). They further demonstrated that distention of one region of the oviduct, the uterus, is followed by increased circulating concentrations of AVT (RZASA et al., 1979). Due to research of Professor Ewy's group, AVT was established to be critically important in causing oviposition or egg lay in the hen.

Among the other areas of the endocrinology of domestic animals pursued by professor Ewy's group were the following:

- Hormonal induction of super-ovulation in cattle (EWY et al., 1985)
- The changes in blood glucose concentrations together hematological parameters during copulation in the boar (EWY et al., 1971; KOLCZAK et al., 1975).

- Effects of environmental temperature of the circulating concentrations of thyroid hormones in birds (BOBEK et al., 1980).

Examination of the role of different sex steroids on the development and growth of the chicken oviduct (MIKA et al., 1987).

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PERSPECTIVES ON GROWTH HORMONE AND METABOLISM IN BIRDS

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Accepted April 27, 2014

Key words: growth hormone, evolution of growth hormone gene, birds

EVOLUTION OF THE GROWTH HORMONE GENE

Origins: The GH-prolactin family of proteins together with that of their receptors is thought to be derived from gene duplication followed by nucleotide substitution (OHTA, 1993). Growth hormone (GH) and the GH-receptor appear to be the ancestral genes for GH/prolactin/somatolactin and the receptor family in early vertebrates approximately 500 million years ago. In Agnatha (e.g. lamprey), there appears to be only GH and its receptor (but not prolactin or its receptor); while both GH and prolactin are found in all gnathostome species (KAWAUCHI and SOWER, 2006; MORIYAMA et al., 2006; ELLENS et al., 2013). It is assumed that the ancestral gene for GH was new to the vertebrate lineage. There is no definitive

evidence for GH or other members of the GH family in invertebrate species. The invertebrates, the cephalochordates (including the present day amphioxus) and urochordates, together with the vertebrates are all derived from a common ancestor diverging about 520 million years ago. There does not appear to be a homolog of GH in the cephalochordate, amphioxus (*Branchiostoma floridae*) genome (HOLLAND et al., 2008). However, both somatostatin and GH immunoreactivity are reported in Hatschek's pit of amphioxus, this being the equivalent of the vertebrate pituitary gland (FANG and WENG, 2006). There are intriguing early reports on the both the presence of GH and effects of GH in proteostome animals, namely mollusks (DOGTEROM et al., 1979; ROUBOS and VAN DE VEN, 1987; WERKMAN et al., 1987).

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Somatolactin: There is another example of a gene duplication of the GH/prolactin genes in fish with somatolactin. This is found in fish: flounder (ONO et al., 1990), Atlantic cod (RAND-WEAVER et al., 1991) and chum salmon (TAKAYAMA et al., 1991) is related to both GH and prolactin. Moreover, there is also a separate somatolactin receptor (FUKAMACHI et al., 2005; FUKAMACHI and MEYER, 2007) which is expressed (RHEE et al., 2012).

Mammalian GH/prolactin gene duplication: There have been a remarkable number of gene duplications of either the GH or prolactin genes in mammals with the vast majority of the duplicated genes being expressed in the placenta (ANTHONY et al., 1995; COOKE and LIEBHABER, 1995; GOOTWINE, 2004; SOARES, 2004; TAKAHASHI et al., 2013). Moreover, there is a very high rate of nucleotide substitution in some of the duplicated genes (WALLIS, 1993).

There have been multiple gene duplications from prolactin gene: rats and mice: 5 placental lactogens, 4 proliferins, 1 proliferin like protein and 20 prolactin related protein genes. Placental lactogens have also been reported in other rodents such as guinea pigs and deer mice (VRANA et al., 2001; ALAM et al., 2010)

Artiodactyles (cattle and sheep: 1 placental lactogen together with 6 prolactin related protein genes).

Gene duplications from GH gene

Catarrhini Primates or Old World monkeys and apes (3 placental lactogens or chorionic somatomammotropins and one GH variant gene expressed in the placenta) and independently.

Platyrrhini Primates or New World monkeys with 3 clusters of genes (LI et al., 2005).

GH, prolactin and placental lactogens are assumed to act via either GH or prolactin receptors (ANTHONY et al., 1995; SOARES, 2004). In addition, placental lactogens and other prolactin-like proteins can have non-classical effects including on immune cells and following proteolytically cleavage on angiogenesis (ANTHONY et al., 1995; SOARES, 2004).

Avian GH/prolactin gene duplication: Until relatively recently, it was viewed that birds have

one GH and one prolactin gene. However, that is not the case. In passerine birds, two genes for GH have been reported (YURI et al., 2008) with both expressed, e.g. jungle crow (ARAI and IGO, 2010) and zebra finch (GenBank Accessions: XM_002196131.2 and XM_004175813.1). What is not known is the functional significance of these duplicated genes and whether there are duplicated GH genes in other avian taxa.

A prolactin-like protein (PLP) has been reported in both birds (chickens and zebra finch) and fish (zebrafish, puffer, green puffer) (WANG et al., 2010). but not in mammals [rat and human] or amphibians [Xenopus – a frog]. The predicted amino-acid residue sequence of chicken PLP has a molecular weight of 22 kDa with an approximate 30% homology with prolactin (PRL) (WANG et al., 2010). Moreover four α helices and three cysteine disulfide bridges are deduced (WANG et al., 2010). PLP is expressed in multiple tissues including broadly in the brain, together with kidney, lung, ovary, muscle and anterior pituitary gland [albeit at a considerably lower level than that of prolactin] in the chicken (WANG et al., 2010). There is a single study reporting increased expression of PLP during cold induced skeletal muscle growth (IJIRI et al., 2013).

Recombinant chicken PLP activate the chicken PRL receptor (cPRLR) (BU et al., 2013) using a 5 \times STAT5-luciferase reporter system with HepG2 cells expressing cPRLR, albeit with a much lower potency than prolactin (BU et al., 2013). What is not known is whether there is a distinct receptor for PLP. This is viewed as likely given the low potency of PLP with the cPRLR (BU et al., 2013) and the relatively low homology between PLP and prolactin (WANG et al., 2010). Other questions about PLP include the following:

- Where is PLP expressed?
- What is the physiological function/significance of PLP?
- Is there post-translational modification of PLP?
- Is PLP released from tissues where there is expression?
- Is PLP found in the circulation?
- Identifying the receptors through which PLP act.

The evolutionary history of the GH/prolactin gene family is summarized in Table 1.

TABLE 1. Evolutionary history of the GH/prolactin gene family

	GH	prolactin	Other members	Last common ancestor
Ancestral Cephalochordates	Not present or lost in descendants	Not present or lost in descendants	Not present or lost in descendants	
Compared to Ancestral Vertebrates	Gained GH gene			891 MYA ^Δ
Primitive Vertebrates (Agnatha)	Present	Not present	Not present	
Compared to Ancestral Gnathostomes	Present	Gained prolactin gene	?	652 MYA ^Δ
Ancestral Actinopterygii (ray finned fish)	Present	Present	Somatolactin and PLP	
Compared to Ancestral Sarcopterygii (ray finned fish and tetrapods)	Present	Present	PLP (Somatolactin either lost or not present at divergence)	430 MYA ^Δ
Ancestors of Mammals/mammalian lineage	Present	Present	PLP lost	
Compared to reptilian ancestors of Birds/Avian lineage	Present + 2nd GH gene in Passerines	Present	PLP	326 MYA ^Δ
Rodents/ruminants/primates	Present	Present	PL	
Compared to Mammalian lineage	Present	Present	Multiple genes duplication of GH or prolactin gene	50 – 65 MYA [†]

^Δ Based on KUMAR and HEDGES, 1998.

[†] Based on KING, 1969.

ACTIONS OF GH

GH, thyroid hormones and avian growth: Both GH and thyroid hormones are essential for the full expression of growth in mammals. The effects of GH are mediated by hepatic and peripherally produced production of insulin-like growth factor-1 (IGF-1). In addition, there is a GH dependent IGF-binding protein 3. Is it reasonable to assume a similar situation exists in birds? The available evidence from studies almost entirely limited to chickens supports a somewhat tentative yes to the question.

Hypophysectomy markedly reduces growth in young chickens (KING, 1969). This is accompanied by loss of all adeno-hypophyseal hormones including GH together with reductions in hormones from target endocrine glands such as thy-

roid hormones (SCANES et al., 1986) and IGF-1 (HUYBRECHTS et al., 1985; LAZARUS and SCANES, 1988). There is some restoration of growth and circulating concentrations of IGF-1 with GH replacement therapy in hypophysectomized chicks (KING and SCANES, 1986; SCANES et al., 1986). Sex linked dwarf chickens do not have abnormally low levels of GH (SCANES et al., 1983). Rather they have markedly depressed levels of triiodothyronine (T_3) (SCANES et al., 1983) and IGF-1 (HUYBRECHTS et al., 1985) due to deficient GH receptors (BURNSIDE et al., 1991). Both growth and plasma concentrations of IGF-1 are markedly depressed in both chickens and turkeys with experimentally induced spiking mortality and concomitant arrest of growth (DAVIS et al., 1995; DAVIS et al., 1997).

The important role of thyroid hormones in avian growth is definitively demonstrated by the suppression of growth in thyroidectomized chicks and the ability of replacement therapy to overcome this (KING and MAY, 1984; MOORE et al., 1984). In addition, T_3 increases growth in hypophysectomized chicks (SCANES et al., 1986). The need for a critical circulating concentration of T_3 is also demonstrated by the ability of moderate doses of T_3 , but not high doses, to stimulate growth in sex-linked dwarf chicks (MARSH et al., 1984). Excessive T_3 is detrimental to growth (KING and MAY, 1984) with T_3 depressing growth in euthyroid chicks (MARSH et al., 1984).

There is considerable cross-talk between the GH and thyroid axes in birds with GH influencing thyroid functioning and thyroid hormones depressing GH secretion (discussed in section below). In chick embryos, GH increases plasma concentrations of T_3 . This effect is via inhibition of hepatic inner ring type III deiodination (KÜHN et al., 1989; KÜHN et al., 1996; VAN DER GEYTEN et al., 1999) and depressed inner ring type III deiodinase expression (VAN DER GEYTEN et al., 1999). The effect of GH is mediated via the GH receptor with GH having little effect in GH receptor deficient sex-linked dwarf chickens (KÜHN et al., 1989). Prolactin depresses plasma thyroxine and elevated ring type III deiodinase (KÜHN et al., 1996). It is not known whether this is mediated by the prolactin receptor. It may be questioned whether the effect of prolactin is acting via the GH receptor as an inverse agonist.

GH and reproduction in birds: There is increasing evidence that GH plays a role in avian reproduction. *In vivo*, GH administration prior to sexual maturity influences ovarian functioning (HRABIA et al., 2011). There are increases follicle number and ovarian weight together with elevated cell proliferation and depressed apoptosis in the stroma and small follicles (HRABIA et al., 2011). Plasma concentrations of GH were elevated in turkey hens during the period of egg laying (SCANES et al., 1979). Some effects of GH on egg shell thickness in laying hens have been reported (DONOGHUE et al., 1990). Moreover, the gonads express GH with GH immunoreactivity and GH mRNA being reported in chicken reproductive tissues: seminiferous tubules (spermatogonia and primary spermatocytes), vas deferens

(HARVEY et al., 2004), ovary granulosa cells (LUNA et al., 2014). Moreover, GHR is co-expressed in chicken granulosa cells (LUNA et al., 2014). *In vitro*, GH stimulates progesterone production by chicken granulosa cells (LUNA et al., 2014). Among the questions remaining is through which receptor the gonadal GH acting. While the predominant gonadal GH is the 17 Da GH variant (LUNA et al., 2014), it is not clear whether this can act via the GH receptor.

There is also evidence that GH has a permissive, or possibly synergistic, role for estrogenic stimulation of vitellogenesis in birds (HARVEY et al., 1979) as well as reptiles (Ho et al., 1972; LORA et al., 2005).

GH and adipose tissue: evidence for effects via different receptors: There is intriguing evidence of at least two distinct receptor types for GH. Both mammalian and avian GH stimulate lipolysis per se while also inhibiting glucagon-stimulated lipolysis (CAMPBELL and SCANES, 1985; CAMPBELL and SCANES, 1987; CAMPBELL et al., 1990). The latter is arguably equivalent to the insulin-like effect of GH in mammals. In contrast, lower vertebrate GHs inhibit glucagon-stimulated lipolysis but are without effect on lipolysis per se (CAMPBELL et al., 1991). The lipolytic effect of GH is inhibited suppressed by a bovine GH antagonist supporting this role being via the GH receptor (CAMPBELL et al., 1993). Unexpectedly, the bovine GH antagonist retains full insulin-like activity; inhibiting glucagon induced lipolysis (CAMPBELL et al., 1993). It is interesting that human placental lactogen is reported to have activities on chicken adipose tissue consistent with it being an inverse agonist (CAMPBELL et al., 1990).

Prolactin, GH and angiogenesis: Proteolytically cleaved prolactin fragment (16K Da) inhibit angiogenesis in chick embryo chorio-allantoic membranes (CAM) and bovine endothelial cells (CLAPP et al., 2012; MORENO-CARRANZA et al., 2013). In contrast, angiogenesis in the CAM is stimulated by chicken GH (GOULD et al., 1995). Among the forms of GH identified in the chicken is a 15 KDa form (ARÁMBURO et al., 2001). What is not clear is whether GH or cleaved fragment of GH influences angiogenesis in the manner that of prolactin perhaps as an inverse agonist (CLAPP et al., 2012).

TABLE 2. Hormonal control of GH expression and secretion

Stimulatory Neuropeptides	Inhibitory Neuropeptides	Stimulatory Peripheral Hormones	Inhibitory Peripheral Hormone
GHRH*	SRIF	Leptin*?	IGF-1
TRH*		Ghrelin?	T ₃
Ghrelin*?			Insulin ^Δ
PACAP*			Glucagon ^Δ
GnRH*?			

* Based on RADECKI et al, 1997, SCANES et al., 2007

^Δ Based on HARVEY et al., 1978

CONTROL OF GH EXPRESSION AND SECRETION

Table 2 summarizes the hormones/neuropeptides influencing GH secretion/expression.

Neuropeptides and GH expression and secretion: Multiple neuropeptides influence GH release and the intra-cellular calcium concentrations within somatotropes, table 2 (SCANES et al., 2007). Examples include the following stimulatory factors: growth hormone releasing hormone (GHRH), thyrotropin releasing hormone (TRH), pituitary adenylated cyclase-activating peptide (PACAP), gonadotropin releasing hormone (GnRH), ghrelin and leptin together with the somatostatin as an inhibitor.

IGF-1 and GH expression and secretion: There is substantial evidence for a negative loop with IGF-1 in birds. Not only does GH increase circulating concentrations of IGF-1 in adult chickens (SCANES et al., 1999; RADECKI et al., 1997), but also in adult female chickens, pituitary expression of GH is suppressed by chronic continuous administration of IGF-1 (SCANES et al., 1999). Further evidence for negative feedback of IGF-1 comes from the elevated circulating concentrations of GH in both young chickens and turkeys with experimentally induced spiking mortality/runting disease and concomitant low circulating concentrations of IGF-1 (DAVIS et al., 1995; DAVIS et al., 1997).

T₃ and GH expression and secretion: A negative feedback loop for GH secretion/expression also exists for the thyroid hormone, T₃. Not only does GH elevate circulating concentrations of T₃

(discussed above) but also T₃ depresses GH secretion and expression (SCANES et al., 1986; RADECKI et al., 1994).

Nutrition and GH

Nutritional deprivation increases circulating concentrations of GH in chickens with effects of short term fasting (HARVEY et al., 1978), chronic protein deprivation (SCANES et al., 1981) and feed restriction (ENGSTER et al., 1979).

Fasting is also associated with the following:

- Depressed circulating concentrations of insulin and lower body temperature (CHRISTENSEN et al., 2013; CHRISTENSEN et al., 2012)
- Depressed circulating concentrations of gonadotropins (SCANES et al., 1976)
- Elevated circulating concentrations of glucagon (CHRISTENSEN et al., 2013)
- Similarly protein deprivation is associated with the following:
- Depressed circulating concentrations of gonadotropins (BUONOMO et al., 1982).

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