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DIVERSIFIED ROLE OF PROLACTIN IN FISH: A REVIEW

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ABSTRACT

Prolactin (PRL), a 198 amino acid long polypeptide hormone, structurally similar to growth hormone and somatotolactin, has one of the widest ranges of action and play crucial roles in regulating various aspects of reproduction and other important function such as osmoregulation, behaviour, growth and development in widely diverge of living lineages. In fish, the main function of PRL is maintenance of water and electrolyte balance but some other functions of PRL were also experimentally observed. In this present review we are focusing on various functional aspects of PRL and trying to present how PRL plays an important role in the maintenance of various life supporting activities in fish.

Key words: Prolactin, Reproduction, Osmoregulation, Behaviour, Fish.

I. INTRODUCTION

Since the discovery of PRL about nine decades ago, extensive research has been performed to explore the role of PRL in various organisms till present day. Prolactin, a widely known anterior pituitary hormone, present in all vertebrates except jawless fish. It has over 300 different well-documented functions (Bole-Feysot et.al, 1998). Experimental studies revealed a conserved function of stimulating milk production in mammals and corporac development in birds. Interestingly PRL also regulate water and ion transport in a variety of tissues of vertebrates. The numerous function of PRL was first summarized by Nicoll and Bern in 1972 they classified different action of PRL into five categories: i) reproduction, ii) osmoregulation, iii) integument, iv) growth and synergism with steroid.

In teleost fish PRL is designated as “freshwater adapting hormone”. The first functional aspect insight into PRL in teleost fish came in the middle of last century. PRL replacement therapy helps in the survival of hypophysectomized killifish (Pickford and Phillips, 1959). It was also well documented the importance of PRL in osmoregulation by acting on osmoregulatory tissues such as gill, kidney, intestine and urinary bladder by ion transport (Hirano, 1986). Besides the osmoregulatory function, PRL also plays an important role in reproduction in various non mammalian vertebrates including fish (Ziegler, 2000).

Fish is one of the most diverse group of vertebrates owing more than 25000 species and offer an important comparative study system for the association between endocrine activity and its physiological effect. Till now the role of PRL in regulation of single physiological activity has been reviewed extensively; in this review we try to focus how PRL alone can exert multi dimensional effects on various physiological activities in fish to maintain their aquatic mode of life.

II. PROLACTIN: STRUCTURE, DISTRIBUTION AND EVOLUTION

PRL is a member of the diverse hormone family that includes growth hormone (GH), somatotolactin and placental lactogen (PL) (Freeman et.al, 2000). The PRL gene is 10kb in length consist of 5 exons and 4 introns. Mammalian PRL is synthesized as a prehormone which is 277amino acids (aa) long including an approximately 28aa long signal peptide (Bole-Feysot et.al, 1998)

About three decades ago a study on Chum salmon (*Oncorhynchus keta*) first reported that the mammalian PRL gene structure is also conserved in piscine family (Kawauchi et.al, 1983). Since then PRL sequences have been isolated

from a wide range of different fish species such as fugu, European eel, rainbow trout, blue gourami (Lee et.al, 2006; Querat et.al, 1994; Mercier et.al, 1989; Degani et.al, 2010). The full length amino acid sequence of PRL has been determined from a variety of teleost and non-teleost fish. Teleost PRL genes are shorter than mammalian PRLs lacking 12-14aa at the N-terminal end and also with a shorter signal sequence (23-24aa) than mammalian signal peptide. Prolactin primarily synthesized and secreted from lactotroph or mammotroph cells located in the anterior pituitary gland in mammals. In addition to that there is also an intermediate cell population designated as mammosomatotrophs capable of secreting both PRL and GH and transformed into lactotrophs in presence of estrogen. In mammals PRL has also been secreted from placenta, uterus, lymphocytes, mammary glands, brain (Freeman et.al, 2000).

In most teleost fishes PRL secreting cells form a definitive mass in the rostral pars distalis of pituitary gland (Clarke and Bern, 2012). Moreover some PRL- immune reactive cells have also been detected in the proximal pars distalis and pars intermedia of teleosts pituitary (Huang and Specker, 1994). In contrast to teleost, the PRL secreting cells of lung fish tend to be distributed throughout the pars distalis with no clear regionalization (Clarke and Bern, 2012). The presence of PRL secreting cells in Agnatha has also been examined. Bioassay and immune cytochemical examination failed to detect PRL in the hagfish pituitary where as PRL- Immunoreactive were observed in the pars distalis of *Petromyzon marinus* (Specker et.al, 1984; Wright,1984). The existence of PRL in the extra pituitary region has also been demonstrated in some fish species. Researchers have detected the presence of PRL like molecules in the preoptic nuclei of *Calamoichthys calabaricus* and also in *Petromyzon marinus* (Hansen and Hansen, 1982; Wright, 1986). Extra Pituitary PRL gene expression has been demonstrated in the liver, gonad and intestine of the sea bream (Santos et.al, 1999) and in the liver, spleen, muscle, gill, gonads of gold fish (Imaoka et.al, 2000)

It is thought that PRL evolved via duplication of an ancestral gene, also gave rise GH, somatolactin, placental lactogen , about 400-800 million years ago (Power, 2005). The isoforms of PRL found in some species, including various fish, evolving through lineage-specific gene duplication or polyploidisation (Huang et.al, 2009; Wallis, 2000). The differences in the disulphide bonding between teleost PRL and other vertebrates suggest that the N-terminal disulphide bond was lost in the common ancestor of teleost fish where as retained in the branch leading to the lobe finned fish and tetrapods (Manjon, 2002). Many organisms have two forms of PRL: PRL1 is commonly found in all vertebrates, in contrast PRL2 has been detected in a number of non-mammalian vertebrates including fish (Huang et.al, 2009)

PRL2 contain three disulfide bond in majority of the cases, evolved through gene duplication in vertebrates after their divergence from the jawless fish. PRL2 can bind with PRL receptor (PRLR , expressed highly in the brain and eye of *Danio rerio* (Huang et.al, 2009). Two different forms of PRL1 were also observed in several fish species including Cichlids and Chum Salmon. These variants are likely to be evolved via lineage specific gene duplication and also differ in their function (Power, 2005)

III. PROLACTIN RECEPTOR

Prolactin receptor (PRLR) belongs from class I cytokine receptor super-family , contain an extracellular ligand binding region, a transmembrane domain and a box 1 domain (Fiol et.al, 2009). In mammals, multiple PRLR isoforms have been found which were formed due to alternative splicing in course of evolution (Manzon, 2002). The first PRLR in teleost fish was cloned in *Oreochromis niloticus* (Sandra et.al,1995) and since then PRL sequences have also been determined for several fish species such as Gold fish, Seabream, Fugu, Blue discus and Starry flounder (Dicky et.al, 2000; Santos et.al, 2001; Lee et.al, 2006; Khong et.al, 2009; Noh et.al, 2012). Similar to the pattern observed for PRL, two isoforms of PRLR (PRLR1 and PRLR2), found in several teleost species, evolved via fish specific gene duplication and exhibit different expression domains (Huang et.al, 2007).

IV. REGULATION OF PRL SECRETION

Till date there are fewer studies have attempted regarding PRL regulatory mechanism in fish. As mentioned earlier PRL is mainly produced from lactotrophs cells of the anterior pituitary and there are several factors that regulate PRL secretion including neurohormones from hypothalamus, steroid hormones and plasma factors produced from other tissues (Kawauchi et.al, 2009).

GnRH neurons that innervate the pituitary that activates membrane bound G-proteins coupled receptors (GPCRs) located on PRL secreting lactotroph cells and producing cellular response (Parhar et.al, 2002). Tipsmark et.al,(2005) demonstrate that, in Mozambique tilapia GnRH activates phospholipase C and inositol triphosphate which leads to mobilization of intracellular calcium and release of PRL from lactotrophs. GnRH treatment in *Oncorhynchus masou masou* pituitary cells elevated pituitary specific transcription factor (Pit-1) which leads to activation of PRL gene promoter in various fishes (Astola et.al, 2003; Boutet et.al, 2007) and was found to synchronizes with elevated PRL mRNA expression. Mature PRL protein binds to the PRLR via to binding sites and results in the dimerization of PRLRs which leads to activation of JAK kinase molecule which in turn phosphorylates STAT, a transcription factor, resulting STAT dimerization. STAT protein then migrates to the nucleus and activates PRL responsive genes. PRL may also cause the activation of MAP kinase pathway (Kawauchi et.al,2009;Bole-Feysot et.al,1998).

V. MULTI DIMENSIONAL ACTIVITIES OF PRL IN FISH PHYSIOLOGY:

5.1. Role of PRL in reproduction:

It has been found that PRL plays an important role in fish reproductive development and sexual maturity. During gonadal development PRL level increases along with gonadotropin in freshwater cat fish (*Clarius batrachus*) and reaches to maximum level during spawning (Singh and Singh, 1981) whereas in Japanese eel no differences in PRL level was found during sexual maturation (Ozaki et.al, 2007). A number of studies have demonstrated that PRL exerts its effect on fish reproductive cycle. PRLR mRNA and protein have been detected in the gonads of various fish species such as Mozambique tilapia, Seabream, Gold fish and Nile tilapia (Edery et.al, 1984; Cavaco et.al,2003; Tse et.al, 2000; Sandra et.al, 2000). PRL may effect spermatogenesis, vitellogenesis and ovulation. PRL levels changes during breeding cycle. Tacon et.al, (2000) demonstrate that in Nile tilapia plasma PRL level in females is highest after spawning. PRL is also involved in steroidogenesis of both male and female fish. PRL directly stimulates testosterone synthesis in Mozambique tilapia and also stimulates 17- β oestradiol production in Guppy (*Poecilia reticulata*) oocytes during their development (Rubin and Specker, 1992, Tan et.al,1988).

5.2. Role in parental care:

It was already known that PRL has a vital role in parental behaviour in mammals and birds (Ziegler, 2000). Mouth brooding is common in several lineages of fish. Recent research in cichlids showed that combinatorial effect of oestrogen and PRL promotes oral egg carrying behaviour (Blum, 1968). In Nile tilapia increased plasma tiPRL177 variance was observed in brooding females though the function of these elevated variance remain unknown (Tacon et.al, 2000).

Several fish species display nest building behaviour. Mucous secretion is associated with nest building is under the regulation of PRL. Experimental administration of PRL increases mucus secretion and also increased the number of mucous cells in paradise fish (*Macropodus opercularis*) (Machemer, 1971; Machemer and Fiedler, 1965). Nest fanning behaviour stimulates a flow of oxygenated water to develop eggs in the nest and this parental fanning activity has been reported to be under the regulation of PRL in various fish species (Pall et.al, 2004). PRL sensitive neurons are found in the forebrain of fish that regulate fanning behaviour (Hoar et.al, 1983).PRL influences a range of other brooding behaviour such as pit-digging, nest guarding and defense (Kindler et.al,1991).

PRL has an evident role in nutrient provisioning in mammals and birds. Nutritive mucus secretion associated with nutrition to offspring is under regulation of PRL. In hypophysectomized guppy and gold fish, administration of PRL

elevated the number of mucus producing cells (Schwerdtfeger, 1979 ; Ogawa, 1970). This parental mucus known as 'discus milk' involved in fry nutrition and offspring or parent immune function (Chong et.al, 2005;2006).

Majority of the research demonstrate a positive relationship between PRL level and brood care, there is one exceptional study on Daffodil cichlids (*Neolamprologus pulcher*) showed that females providing brood care have lower PRL mRNA expression than non brooding one (Bender et.al, 2008).

5.3. Role in migration:

Migration plays an important role in many aspects of life cycle of vertebrates. In fish migration is associated with reproductive cycle of several species. In chum salmon PRL mRNA expression is increased with the onset of anadromous migration (Onuma et.al.,2010). It is assumed that this effect maybe due to osmoregulatory function of PRL necessary for the transition from salt water to fresh water but experiments demonstrated that pre-spawning fish reared in salt water also shows elevated PRL mRNA expression in the final stage of maturation (Onuma et.al.,2003). Similarly in *Anguilla japonica* PRL mRNA expression is reduced when the fish mature and migrate downstream where as in sticklebacks (*Gasterosteus aculeatus*) PRL level increased during migration from saline water to fresh water (Whittington and Wilson, 2013). These facts highlight that PRL is related with the migratory behaviour in many fish.

5.4. Role in immunomodulation:

Research regarding role of PRL in fish immune system is relatively recent. It is evident that PRL is an important modulator of fish immune function. It enhances the immunoglobulin production and phagocytic activity of leucocytes, also exerts mitogenic effects on leucocytes (Yada et.al, 1999; Sakai et.al, 1996; Yada et.al, 2004).

5.5. Role in egg and larval development:

Till date there are relatively few studies have been done regarding the role of PRL in fish development. However in Seabream presence of PRL mRNA is detected and gradually elevated during somitogenesis and embryogenesis respectively (Santos et.al, 2003). In mozambique tilapia PRL transcripts are detected soon after fertilization and markedly increase during the time of gastrulation (Santos et.al, 2003; Shiraishi et.al, 1999). This sudden increment in the PRL concentration during gastrulation raises the questions regarding the involvement of PRL in fish organogenesis (Kimmel et.al, 1990). The role of PRL in the osmoregulation of egg is yet to be studied. An in vitro experiment demonstrated that chloride cells of fish embryo respond to the changes in salinity through autonomous regulation (Kaneko et.al, 2002). However the mechanism of PRL action in regulating egg osmoregulation remains to be detected (Santos et.al, 2003)

5.6. Role in osmoregulation:

Freshwater fish face two primary challenges: inhibiting ion loss to the external to the hypoosmotic environment and preventing influx of water. PRL plays a giant role in the regulation of these activities during the adaptation period. Gill is the one of the main site for the regulation of ion and water exchange. This is well established that chloride cells play a central role in the chloride ion balance of fresh water fish; PRL appears to have a prominent effect on the number, morphology and distribution of chloride cells. Receptor for PRL have also been found in the chloride cells of *Oreochromis mossambicus* (McCormick, 1995; Weng et.al,1997). The main threat to freshwater fish is the loss of ion by diffusion and regulation of water balance is the secondary in importance with regards to freshwater survival. Experimental studies demonstrated that PRL lowered the osmotic permeability of the gills and also increase the mucus secretion that may help in the regulation of water and ion balance by impeding the passage of molecules in and out of the gill cells (Brown and Brown,1987; Horseman, 1987; Bentley, 1998). PRL increases sodium ion reabsorption and water excretion. Although how PRL exerts this effects is yet to be fully understood. Specific PRLR was observed in the kidney and recent studies have demonstrated that PRL administration increased the renal Na^+/K^+ ATPase activity in hypophysectomized *Fundulus heteroclitus* (Epstein et.al, 1969) In addition to that PRL elevate the urine output by increasing glomerular filtration rate and also lowered the urine osmolality (Clarke and Bern, 1980)

Earlier studies demonstrated that PRL lowered the Na^+ , Cl^- and water absorption in intestine (Colie and Hirano, 1987). Administration of ovine PRL decreases the intestinal fluid and salt absorption in Japanese eel and in trout but interestingly opposite effect was observed in the anterior intestine of *Oreochromis mossambicus* (Utida et.al, 1972; Morley et.al, 1981; Mainoya 1982). Recent experimental studies shown that ovine PRL administration increases the Na^+/K^+ ATPase activity in *Sparus sarba* (Kelly et.al, 1999).

The osmoregulatory action of PRL is closely associated to its hypercalcemic action. PRL enhances the calcium absorption in branchial tissue (Anderson and Itallie, 2009). In *Oreochromis mossambicus* PRL administration promote the gill calcium influx also simultaneously inhibit the calcium efflux results in hypercalcemia (Flik et.al, 1994). PRL also enhance Calcium accretion in bones and scales of female gold fish (Takahashi et.al, 2008).

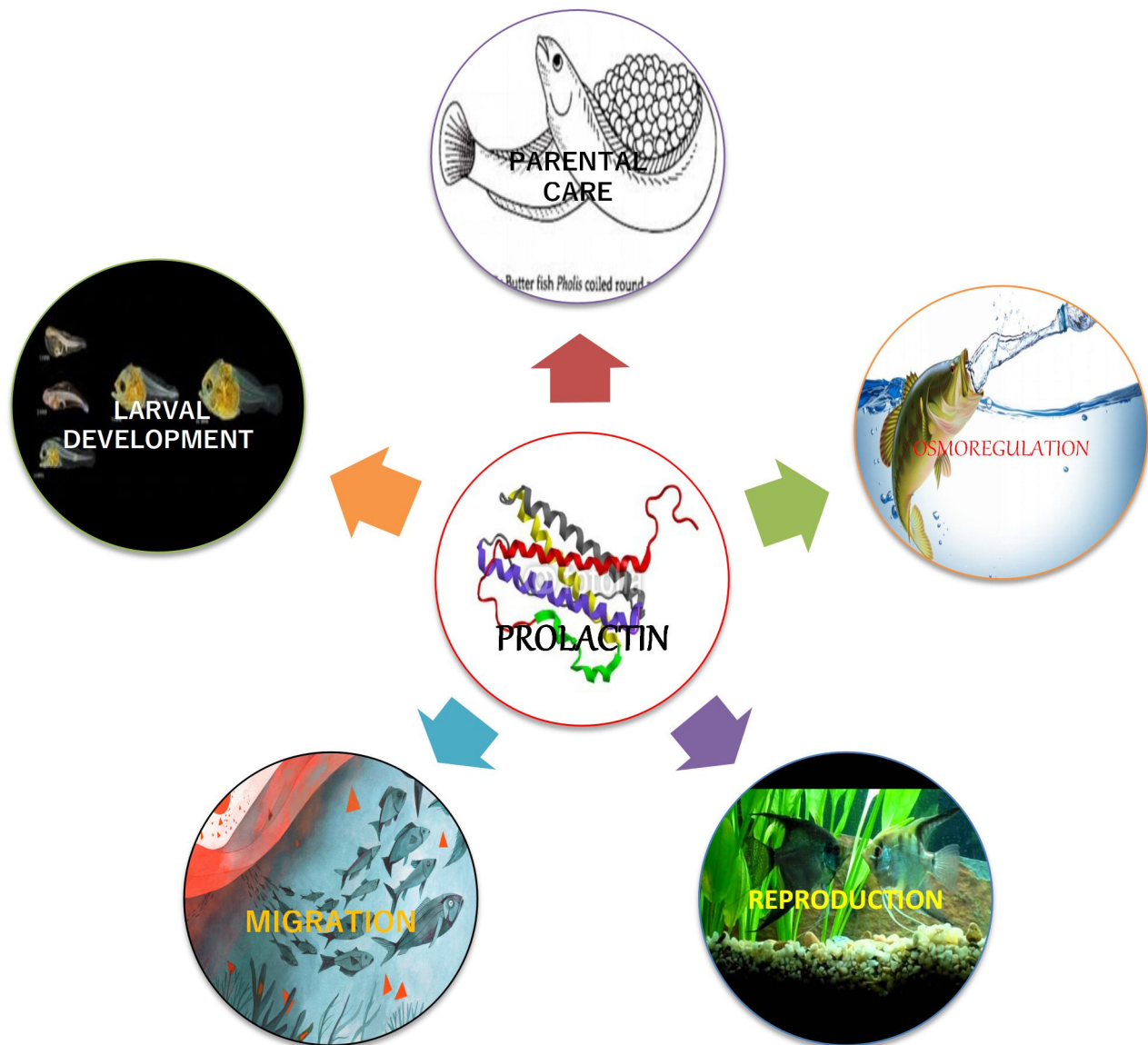


Fig.1: Multi-directional role of prolactin in fish

VI. CONCLUSION

In summary the current review has shown that PRL has multiple functions in diverse group of fishes and probably also in the larval stages of their life. Study of PRL action from comparative aspect of fishes has clearly identified that PRL is the key hormonal regulator of ion and water transport but it has been evident from the above discussions that PRL also have other wide array of diversified physiological functions in the life of fish.

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