

Mini Review

Modulation of the fish immune system by hormones

James Harris^{*}, David J. Bird

Faculty of Applied Sciences, University of the West of England, Bristol, BS16 1QY, UK

Accepted 6 September 2000

Abstract

Immune–neuroendocrine interactions in fish, as in mammals, have become a focus of considerable interest, with the modulation of immune responses by hormones receiving particular attention. Cortisol, growth hormone (GH), prolactin (PRL), reproductive hormones, melanin-concentrating hormone (MCH) and proopiomelanocortin (POMC)-derived peptides have all been shown to influence immune functions in a number of fish species. This review summarises the known effects of these hormones on the fish immune system, as well as the often complex interactions between different hormones. The possible implications for fish health, with respect to aquaculture and the changes in immunocompetence that take place during different stages in the fish life cycle are also discussed. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Neuroendocrine system; Fish immune system; Hormones; Stress; POMC

1. Introduction

In recent years, it has become increasingly apparent that the mammalian immune and neuroendocrine systems are intimately linked and that bi-directional communication between the two is essential for the maintenance of homeostatic function. The majority of studies have concentrated on the interaction between the two systems via cytokines and neuropeptides and as a result it has become difficult to define many of these molecules simply in terms of the function with which they were originally associated. More recently, immune–endocrine interactions in non-mammalian vertebrates, especially fish, have received increased attention. The aim of this review is to summarise some of these interactions, with emphasis on the effects of circulating hormones, including cortisol, reproductive hormones, growth hormone (GH) and prolactin (PRL) and some proopiomelanocortin (POMC)-derived peptides on fish immune responses (see Table 1).

^{*} Corresponding author. Present address: Division of Immunology and Pathology, Institute for Animal Health, Compton, near Newbury, Berkshire, RG20 7NN, UK. Tel.: +44-1635-578411; fax: +44-1635-577237.
E-mail address: james.harris@bbsrc.ac.uk (J. Harris).

Table 1
Stimulatory (+) and inhibitory (–) effects of various hormones on immune responses in teleost fish

Hormone	Phagocytosis	Respiratory burst	Mitogenesis
Cortisol	–		–
GH	+	+	+
PRL	+	+	+
11-Ketotestosterone			–
Oestradiol			+
α -MSH	+	+	+/–
MCH	+	+	+
β -EP	+	+	
ACTH		+	–

2. Immunomodulatory effects of hormones

2.1. Cortisol

The primary corticosteroid produced in the teleost interrenal gland is cortisol and, unlike in mammals, there is little evidence for significant synthesis of corticosterone or cortisone (Kime, 1987). The immunomodulatory effects of stress and corticosteroids in mammals are well documented (Ader et al., 1991; Sternberg et al., 1992; Stein and Miller, 1993) and comparable effects have been observed in fish (for a review, see Schreck, 1996). For example, a number of studies have shown that stress or cortisol administration decreases the resistance of fish to bacterial and fungal pathogens (Maule et al., 1989; Pickering and Pottinger, 1989; Wiik et al., 1989).

Most studies in fish have focused on the effects of cortisol administration on the immune system, both in vitro and in vivo (Table 2), although the release of catecholamines is also of significance, as they have immunomodulatory effects, including depressed phagocytic responses (Narnaware et al., 1994; Narnaware and Baker, 1996). Cortisol administration has been shown to reduce the number of circulating T- and B-like lymphocytes (McLeay, 1973a; Pickering, 1984; Pulsford et al., 1994), while the number of circulating phagocytes (neutrophils and macrophages) may increase (Pulsford et al., 1994). The fate of lymphocytes following stress is unclear, although re-trafficking of cells to lymphoid tissues may be involved. Thus, acute stress or cortisol treatment in juvenile coho salmon (*Oncorhynchus kisutch*) lowers the number of circulating leukocytes, but increases the number of these cells in the thymus and head kidney (Maule and Schreck, 1990a). Cortisol, however, has also been shown to induce apoptosis in B cells and this could be responsible for their clearance from the blood following stress (Weyts et al., 1997, 1998a; Verburg-van Kemenade et al., 1999).

Cortisol has depressive effects on a number of immune responses in fish, including phagocytosis and lymphocyte mitogenesis (Table 2). In addition, cortisol decreases the activity of antibody producing cells and circulating titres of IgM (Maule et al., 1989; Nagae et al., 1994). The effects of cortisol are mediated via the glucocorticoid receptor (GR), which has been identified in leukocytes from coho salmon and carp (*Cyprinus carpio*) (Maule and Schreck, 1990b; Ducouret et al., 1995; Weyts et al., 1998b).

Table 2
Effects of cortisol on immune functions in fish

Effect	Species	References
Reduced number of circulating lymphocytes	<i>Oncorhynchus kisutch</i>	McLeay (1973b)
	<i>Salmo trutta</i>	Pickering (1984)
	<i>Ictalurus punctatus</i>	Ellsaesser and Clem (1986)
	<i>Limanda limanda</i>	Pulsford et al. (1994)
	<i>Salmo salar</i>	Epselid et al. (1996)
	<i>Oncorhynchus mykiss</i>	Narnaware and Baker (1996)
Decreased lymphocyte proliferation	<i>Pleuronectes platessa</i>	Grimm (1985)
	<i>Ictalurus punctatus</i>	Ellsaesser and Clem (1986)
	<i>Oncorhynchus kisutch</i>	Tripp et al. (1987)
	<i>Limanda limanda</i>	Pulsford et al. (1994)
	<i>Cyprinus carpio</i>	Weyts et al. (1997)
Decreased antibody production/numbers of antibody-producing cells	<i>Oncorhynchus mykiss</i>	Anderson et al. (1982)
	<i>Cyprinus carpio</i>	Ruglys (1985)
	<i>Oncorhynchus kisutch</i>	Tripp et al. (1987)
	<i>Oncorhynchus tshawytscha</i>	Maule et al. (1989)
	<i>Pleuronectes americanus</i>	Carlson et al. (1993)
Decreased phagocytosis	<i>Limanda limanda</i>	Pulsford et al. (1995)
Increased apoptosis	<i>Cyprinus carpio</i>	Weyts et al. (1997, 1998a)
	<i>Oreochromis mossambicus</i>	Bury et al. (1998)

2.2. Growth hormone and prolactin

Growth hormone and prolactin are widespread vertebrate polypeptides that are produced in the adenohypophysis of the pituitary gland and show many structural and functional similarities. In all vertebrates, GH is involved in the regulation of post-natal somatic growth, but in fish it also influences osmoregulation and stimulates gonadal steroidogenesis (Sakai et al., 1996b). Prolactin is a versatile peptide with diverse functions that may be summarised under three broad categories of growth and development, osmoregulation and reproduction (Batten and Ingleton, 1987; Sakai et al., 1996b; Prunet et al., 1989). Both hormones have also been implicated in the modulation of immune responses in vitro and in vivo. Indeed, GH is structurally similar to a number of cytokines, including interleukin (IL)-2, IL-4, IL-5, granulocyte-colony stimulating factor, granulocyte-macrophage colony-stimulating factor and the interferons (Sprang and Bazan, 1993).

In mammals, GH and PRL stimulate thymocyte maturation and differentiation and activate phagocytes (Edwards et al., 1992; Warwick-Davies et al., 1995; Ortega et al., 1996) and GH counters glucocorticoid-induced apoptosis of T cell progenitors (Murphy and Longo, 2000). Similarly, in fish, GH has been shown to stimulate lymphopoiesis and phagocytosis in gilthead sea bream (*Sparus aurata*) and silver sea bream (*Sparus sarba*) (Calduch-Giner et al., 1995, 1997; Narnaware et al., 1997). It also enhances leukocyte mitogenesis in chum salmon (*Oncorhynchus keta*) (Sakai et al., 1996b), phagocytosis, natural killer cell activity, antibody production and serum haemolytic activity in rainbow

trout (*Oncorhynchus mykiss*) (Kajita et al., 1992; Sakai et al., 1995, 1996a; Yada et al., 1999) and respiratory burst activity of leukocytes in rainbow trout and Mediterranean sea bass (*Dicentrarchus labrax*) (Sakai et al., 1996c; Kitlen et al., 1997; Muñoz et al., 1998). Other studies have shown that the peptide enhances the resistance of rainbow trout to the bacterial pathogen *Vibrio anguillarum* in vivo (Sakai et al., 1997). In addition, transferring brown trout (*Salmo trutta*) from freshwater to seawater increases plasma titres of GH while reducing titres of thyroid hormones and this has been correlated with increased phagocytic activity of head kidney leukocytes and elevated plasma lysozyme concentrations (Marc et al., 1995). Prolactin has similar effects on fish immune responses and has been shown to stimulate leukocyte mitogenesis (Sakai et al., 1996b), respiratory burst activity (Sakai et al., 1996c) and phagocytosis (Narnaware et al., 1998) and to increase plasma IgM titres (Yada et al., 1999).

2.3. Reproductive hormones

Although in mammals androgens are predominantly associated with male and estrogens with female reproductive functions, this is not the case in fish. While many of the steroids identified in the teleost ovary are the same as those secreted in mammals, testosterone and androstenedione are major products in female fish (Scott, 1987). Steroidogenesis in the teleost testis also differs from most other vertebrates with 11-ketotestosterone or 11 β -OH testosterone often being the most potent androgens (Scott, 1987).

In mammals, oestradiol enhances the activity of splenic macrophages (Schreiber et al., 1988), but inhibits the production of natural killer cells (Seaman et al., 1978). This steroid also stimulates the antibody response (Stoeger et al., 1988) and IL-1 synthesis (Hu et al., 1988). Testosterone, on the other hand, inhibits the antibody response and interferes with lymphocyte transformation (Wyle and Kent, 1977; Stoeger et al., 1988). Similar effects have been observed in rainbow trout with oestradiol and 11-ketotestosterone, which cause stimulation and inhibition of lymphocyte proliferation, respectively (Cook, 1994). Testosterone also reduces the number of antibody-producing cells in fish and synergises with cortisol to produce a greater inhibitory effect, suggesting that the two hormones act independently on different cells (Slater and Schreck, 1993). In addition, Slater and Schreck (1997) have demonstrated that testosterone can kill salmonid leukocytes in vitro, which may be a mechanism behind at least some of the immunosuppressive effects of the hormone. Recently, the characterisation of receptors for reproductive hormones on salmonid leukocytes has provided further evidence for an immunoregulatory role of these steroids in fish (Slater et al., 1995; Patino and Maule, 1997).

During their freshwater migration and sexual maturation, salmonids display high plasma levels of the gonadal steroids, oestradiol, testosterone, 11-ketotestosterone and androstenedione (Maule et al., 1996). Sexually mature salmonids (both male and female) demonstrate immune deficiencies at this time in their life cycle that include an inability to produce iso-haemagglutinins, antibodies that are produced in immature fish (Ridgeway, 1962) and are subject to an increased frequency of ectoparasitic infestations, particularly the males (Pickering and Christie, 1980). Related to these observations is the fact that rainbow trout serum shows reduced bactericidal activity during spawning (Iida et al.,

1989). However, Maule et al. (1996) examined specific and non-specific immune responses in Pacific salmon during their freshwater migration and sexual maturation and found positive correlations between plasma gonadal steroid levels and both serum lysozyme activity and antibody-producing cell numbers, but it is not clear if this is the result of a direct casual link, since they also correlated with the date of sampling (Maule et al., 1996).

2.4. Melanotropins and POMC-derived peptides

In teleost fish, the melanotropins α -melanocyte stimulating hormone (α -MSH) and melanin-concentrating hormone (MCH) modulate the hormonal control of skin colour. Both peptides are released from the pituitary gland and exert their effects directly on melanophores, α -MSH causes dispersion of melanin granules and thus darkening the skin, while MCH has the opposite effect, concentrating melanin granules and inducing skin pallor (Rance and Baker, 1979; Eberle, 1988). In this role, the two peptides are mutually antagonistic (Baker, 1991). Both peptides have also been implicated in a number of physiological functions in fish and mammals, including the regulation of the hypothalamo-pituitary-adrenal (HPA) axis, feeding, the response to auditory stimuli, osmoregulation and various behaviours (Miller et al., 1993; Baker, 1994; Gonzalez et al., 1996; Ludwig et al., 1998; Gilchrist et al., 1999).

In mammals, α -MSH is a potent modulator of immune responses. The peptide inhibits fever and all major forms of inflammation (Lipton and Catania, 1997), and exerts its effects both by direct interaction with immunocompetent cells in peripheral tissues and by modulation of neuronal pathways within the central nervous system (Watanabe et al., 1993; Ceriani et al., 1994). The anti-inflammatory effects of α -MSH appear to be largely directed through the modulation of cytokine synthesis, release and action. In particular, the peptide inhibits the pro-inflammatory effects of IL-1, IL-6, IL-8 and TNF α (Shih et al., 1986; Taylor et al., 1992; Ceriani et al., 1994) and stimulates the production and release of the anti-inflammatory cytokine, IL-10 (Bhardwaj et al., 1996). Alpha-MSH also inhibits a number of cellular functions in vitro, including neutrophil chemotaxis and the release of nitric oxide (NO) and neopterin from monocytes/macrophages (Star et al., 1995; Catania et al., 1996; Rajora et al., 1996). In addition, the peptide has direct antimicrobial effects against *Candida albicans* and *Staphylococcus aureus* (Cutuli et al., 2000) and enhances the production of IgE, IL-6 and TNF α by human PBMCs (Aebischer et al., 1994). The effects of MCH on immune responses in mammals have not yet been investigated, although expression of MCH mRNA has been reported in a number of immunological tissues in the rat, including the spleen (Nahon et al., 1993; Drodz and Eberle, 1995).

Early evidence for an immunoregulatory role of melanotropins in fish comes from a report by Sumner and Doudoroff (1938), who found that fish kept in dark tanks were more susceptible to infectious diseases than those kept in light tanks. Later, Bowley et al. (1983) showed that fish infected with furunculosis have increased plasma titres of α -MSH and recent studies on rainbow trout have shown that both α -MSH and MCH stimulate the proliferation of rainbow trout head kidney leukocytes in vitro (Harris and Bird, 1997). Similar investigations by Cook (1994) demonstrate that

MCH stimulates the proliferation of trout head kidney and splenic leukocytes, though in the same study α -MSH had no effect. Both peptides have also been shown to stimulate the phagocytic and respiratory burst activity of trout head kidney phagocytes in vitro (Harris and Bird, 1998, 1999; Harris et al., 1998), while α -MSH, *N*-des-acetyl- α -MSH and di-acetyl- α -MSH stimulate superoxide production by carp phagocytes in vitro (Takahashi et al., 1999, 2000). When cultured with supernatants derived from leukocytes that had been exposed to either α -MSH or MCH, the activity of trout phagocytes in vitro is stimulated, suggesting that the peptides trigger the release of a macrophage-activating factor (MAF) (Harris and Bird, 2000). These effects are not straightforward however, since α -MSH and MCH are mutually antagonistic on both mitogenesis and phagocytic activity when added simultaneously (Harris and Bird, 1997, 1998). The effects of α -MSH on mitogenesis appear to be strongly concentration-dependent, with inhibition at low concentrations and stimulation at higher concentrations (Harris and Bird, 1999). In view of this bi-phasic action of α -MSH, it is interesting that MCH has a similar dual action on α -MSH release from the pituitary gland of tilapia (*Oreochromis mossambicus*) in vitro (Gröneveld et al., 1995). MCH also reduces the inhibitory effects of cortisol on mitogenesis (Cook, 1994), although it is not clear whether this is due to antagonism between the two hormones or the result of mixed inhibitory/stimulatory signals.

The expression of the MC-1 receptor, specific for α -MSH, has been detected on human neutrophils, dendritic cells and monocytes/macrophages (Catania et al., 1996; Rajora et al., 1996; Becher et al., 1999) and on murine mast cells (Adachi et al., 1999), and the peptide itself is produced by rat splenocytes and human monocytes (Rajora et al., 1996; Jessop et al., 1994). Thus, in mammals, α -MSH may exert some of its effects in peripheral tissues through localised paracrine or autocrine release. No studies have yet determined whether fish immunocytes express MC-1 or the recently discovered MCH receptor, SLC-1 (Bachner et al., 1999; Chambers et al., 1999; Lembo et al., 1999; Saito et al., 1999; Shimomura et al., 1999).

Cleavage of the precursor molecule POMC can give rise to a number of bioactive peptides that include not only α -MSH, but also β - and γ -MSH, ACTH and β -endorphin (β -EP). In addition, a fourth MSH (termed δ -MSH) has been identified in elasmobranchs (Amemiya et al., 1999). Like α -MSH, ACTH and β -EP have been implicated in modulating immune responses in fish and all three have been detected immunocytochemically in goldfish leukocytes (Ottaviani et al., 1995). It has been shown, also, that immunoreactive ACTH is secreted by catfish blood mononuclear cells and lymphocytes (Arnold and Rice, 1997) and that immunoreactive α -MSH is released from tilapia head kidney tissue cultures (Balm et al., 1995). Since all these studies are based on the use of antibodies, they are subject to potential artifacts from cross-reactivity with other antigens and further confirmatory evidence will be required (Weyts et al., 1999).

In mammals, β -EP has been shown to augment the activation of macrophages and neutrophils (Sharp et al., 1985; Hagi et al., 1994) and stimulate T cell proliferation (Van Epps and Saland, 1984). In fish, this opioid stimulates phagocytic and respiratory burst activity of rainbow trout phagocytes in vitro, both directly and after intraperitoneal injection (Watanuki et al., 1999, 2000). Similarly, β -, γ - and δ -MSH have all been shown to stimulate superoxide production by carp head kidney phagocytes in vitro (Takahashi

et al., 1999, 2000), while ACTH decreases circulating leukocyte numbers (McLeay, 1973b), inhibits lymphocyte mitogenesis (Weyts et al., 1999) and increases phagocyte respiratory burst activity in fish (Bayne and Levy, 1991). In humans, this peptide has been shown to enhance production of IL-6 and TNF α and exert both stimulatory and inhibitory effects on IgE synthesis by PBMCs in the presence of IL-4 and anti-CD40 monoclonal antibody (Aebischer et al., 1994).

3. Concluding remarks

Fish provide a useful model for studying immune–endocrine interactions that complements our knowledge of the way these systems are linked in mammals. A comparison of the interactions in different vertebrate groups can help elucidate their physiological significance and shed light on how the association between the immune and endocrine systems has evolved.

In view of the complex *mêlée* of hormones present in the circulation of fish under different physiological and environmental conditions, the interplay between different hormones and the immune system *in vivo* is difficult to determine. Since most hormones have been shown to affect the synthesis and release of other hormones, the situation is likely to be very complex. It is already apparent, for example, that the release of MCH and α -MSH is intimately linked and that both peptides modulate the release of luteinising hormone in rats, which is itself produced by human leukocytes (Baker, 1991; Gonzalez et al., 1997; Hotakainen et al., 2000). Indeed, the effects of stress on the immune system are difficult to interpret simply in terms of cortisol/catecholamine immunosuppression, as a number of different hormones are involved via the HPA axis, including corticotrophin-releasing factor and ACTH (which, in turn, affect the release of other hormones). Thus, it is likely that immunological responses to stress are dependent on the actions of various hormones, their interactions with each other, with immunocompetent cells as well as with other endogenous factors, such as cytokines.

Many fish species go through distinct life cycle stages that are associated with changes in the levels of circulating hormones. The interactions between different hormones are often complex, but in many cases changes in plasma hormone levels correspond with changes in the immune status and health of the fish (Fig. 1). The modulatory effects of hormones on fish immune responses may have important implications for fish health and aquacultural practice and the study of these effects may lead to a better understanding of the interactions between the immune and endocrine systems in other animals, including mammals.

In fish, the potential immunomodulatory effects of other hormones associated with physiological and environmental adaptation have yet to be investigated, particularly the role of angiotensin II, the thyroid hormones, as well as other opioids, such as methionine-enkephalin, a peptide that is known to be a potent immunomodulator in invertebrates and mammals (Plotnikoff et al., 1997; Stefano and Salzet, 1999). While endocrine effects of circulating hormones may modulate general immunological competence, local paracrine and autocrine effects are likely to be more significant. This has already been shown to be the case in mammals, where local secretion of ACTH and α -MSH can have subtle

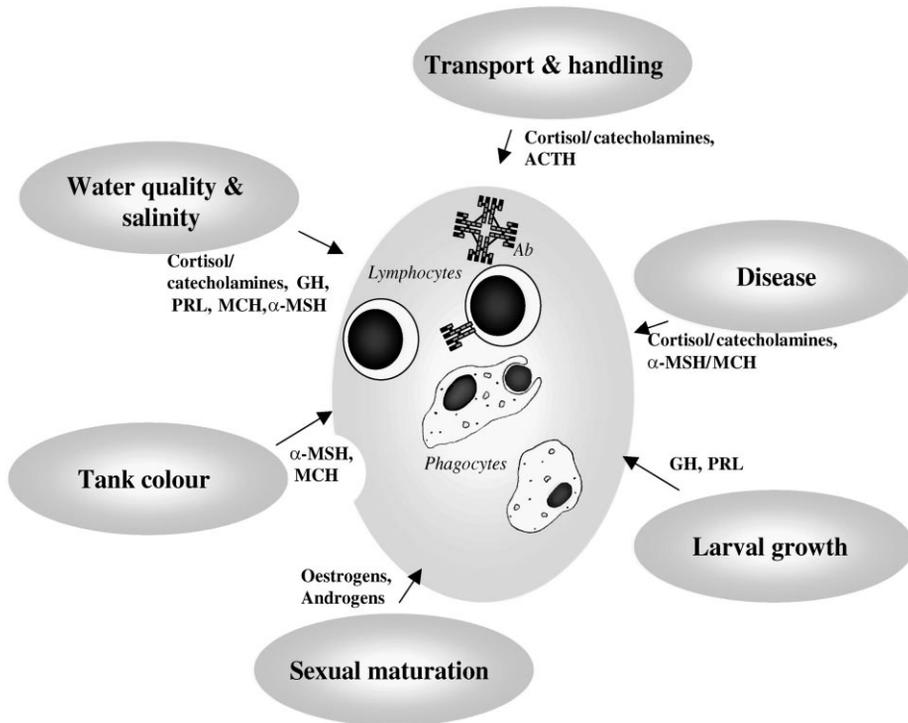


Fig. 1. Known and putative immune–endocrine interactions with respect to aquaculture processes and different life stages in fish.

immunological actions and there is little doubt similar effects will be found to occur in fish.

Future research is likely to involve further application of mRNA probes to identify whether immunological cells are capable of synthesising specific messenger molecules. This will help establish the importance of ‘local’ secretion by different cell types while the identification of specific hormone receptors on these cells will confirm their capacity to respond to these ubiquitous messenger molecules.

Acknowledgements

We would like to thank Bridget Baker and Julie Mcleod for their helpful comments on the manuscript.

References

- Adachi, S., Nakano, T., Vliagoftis, H., Metcalfe, D.D., 1999. Receptor-mediated modulation of murine mast cell function by alpha-melanocyte stimulating hormone. *J. Immunol.* 163, 3363–3368.

- Ader, R., Felten, D.L., Cohen, N. (Eds.), 1991. Psychoneuroimmunology, 2nd edition. Academic Press, San Diego.
- Aebischer, I., Stämpfli, M.R., Zürcher, A., Miescher, S., Urwyler, A., Frey, B., Luger, T., White, R.R., Stadler, B.M., 1994. Neuropeptides are potent modulators of human in vitro immunoglobulin E synthesis. *Eur. J. Immunol.* 24, 1908–1913.
- Amemiya, Y., Takahashi, A., Suzuki, N., Sasayama, Y., Kawachi, H., 1999. A newly characterised proopiomelanocortin in pituitaries of an elasmobranch, *Squalus acanthias*. *Gen. Comp. Endocrinol.* 114, 387–395.
- Anderson, D.P., Roberson, B.S., Dixon, O.W., 1982. Immunosuppression induced by a corticosteroid or an alkylating agent in rainbow trout (*Salmo gairdneri*) administered a *Yersinia ruckeri* bacterin. *Dev. Comp. Immunol.* S2, 197–204.
- Arnold, R.E., Rice, C.D., 1997. Channel catfish lymphocytes secrete ACTH in response to corticotropin releasing factor (CRF). *Dev. Comp. Immunol.* 21, 152.
- Bachner, D., Kreienkamp, H.J., Weise, C., Buck, F., Richter, D., 1999. Identification of melanin-concentrating hormone (MCH) as the natural ligand for the orphan somatostatin-like receptor 1 (SLC-1). *FEBS Lett.* 457, 522–524.
- Baker, B.I., 1991. Melanin-concentrating hormone: a general vertebrate neuropeptide. *Int. Rev. Cytol.* 126, 1–47.
- Baker, B.I., 1994. Melanin-concentrating hormone updated. Functional considerations. *Trends Endocrinol. Metabol.* 5, 120–126.
- Balm, P.H.M., van Lieshout, E., Lokate, J., Wendelaar Bonga, S.E., 1995. Bacterial lipopolysaccharide (LPS) and interleukin 1 (IL-1) exert multiple physiological effects in the tilapia *Oreochromis mossambicus* (Teleostei). *J. Comp. Physiol. B* 165, 85–92.
- Batten, T.F.C., Ingleton, P.M., 1987. The structure and function of the hypothalamus and pituitary gland. In: Chester-Jones, I., Ingleton, P., Phillips, J.G. (Eds.), *Fundamentals of Comparative Vertebrate Endocrinology*. Plenum Press, New York, pp. 285–408.
- Bayne, C.J., Levy, S., 1991. The respiratory burst response of rainbow trout *Oncorhynchus mykiss* (Waldbaum), phagocytes is modulated by sympathetic neurotransmitters and the 'neuro' peptide ACTH. *J. Fish Biol.* 38, 609–619.
- Becher, E., Mahnke, K., Brzoska, T., Kalden, D.H., Grabbe, S., Luger, T.A., 1999. Human peripheral blood-derived dendritic cells express functional melanocortin receptor MC-1R. *Ann. NY Acad. Sci.* 885, 188–195.
- Bhardwaj, R.S., Schwarz, A., Becher, E., Mahnke, K., Aragane, Y., Schwarz, T., Luger, T.A., 1996. Proopiomelanocortin-derived peptides induce IL-10 production in human monocytes. *J. Immunol.* 156, 2517–2521.
- Bowley, T.J., Rance, T.A., Baker, B.I., 1983. Measurement of immunoreactive α -melanocyte-stimulating hormone in the blood of rainbow trout kept under various conditions. *J. Endocrinol.* 97, 267–275.
- Bury, N.R., Jie, L., Flik, G., Lock, R.A.C., Wendelaar Bonga, S.E., 1998. Cortisol protects against copper induced necrosis and promotes apoptosis in fish gill chloride cells in vitro. *Aquatic Toxicol.* 40, 193–202.
- Calduch-Giner, J.A., Sitjà-Bobadilla, A., Alvarez-Pellitero, P., Pérez-Sánchez, J., 1995. Evidence for a direct action of GH on haemopoietic cells of a marine fish, the gilthead sea bream (*Sparus aurata*). *J. Endocrinol.* 146, 459–467.
- Calduch-Giner, J.A., Sitjà-Bobadilla, A., Alvarez-Pellitero, P., Pérez-Sánchez, J., 1997. Growth hormone as an in vitro phagocyte-activating factor in the gilthead sea bream (*Sparus aurata*). *Cell Tiss. Res.* 287, 535–540.
- Carlson, R.E., Anderson, D.P., Bodammer, J.E., 1993. In vivo cortisol administration suppresses the in vitro primary immune response of winter flounder lymphocytes. *Fish Shellfish Immunol.* 3, 299–312.
- Catania, A., Rajora, N., Capsoni, F., Minonzio, F., Star, R.A., Lipton, J.M., 1996. The neuropeptide α -MSH has specific receptors on neutrophils and reduces chemotaxis in vitro. *Peptides* 17, 675–679.
- Ceriani, G., Macaluso, A., Catania, A., Lipton, J.M., 1994. Central neurogenic antiinflammatory action of α -MSH: modulation of peripheral inflammation induced by cytokines and other mediators of inflammation. *Neuroendocrinology* 59, 138–143.
- Chambers, J., Ames, R.S., Bergsma, D., Muir, A., Fitzgerald, L.R., Hervieu, G., Dytko, G.M., Foley, J.J., Martin, J., Liu, W.-S., Park, J., Ellis, C., Ganguly, S., Konchar, S., Cluderay, J., Leslie, R., Wilson, S., Sarau, H.M., 1999. Melanin-concentrating hormone is the cognate ligand for the orphan G-protein-coupled receptor SLC-1. *Nature* 400, 261–265.

- Cook, J., 1994. The effects of stress, background colour and steroid hormones on the lymphocytes of rainbow trout (*Oncorhynchus mykiss*). Ph.D. Thesis, University of Sheffield.
- Cutuli, M., Cristiani, S., Lipton, J.M., Catania, A., 2000. Antimicrobial effects of alpha-MSH peptides. *J. Leukoc. Biol.* 67, 233–239.
- Drodz, R., Eberle, A.N., 1995. Binding sites for melanin-concentrating hormone (MCH) in brain synaptosomes and membranes from peripheral tissues identified with highly tritiated MCH. *J. Rec. Sig. Trans. Res.* 15, 487–502.
- Ducouret, B., Tujague, M., Ashraf, J., Mouchel, N., Serval, N., Valotaire, Y., Thompson, E.B., 1995. Cloning of a teleost fish glucocorticoid receptor shows that it contains a deoxyribonucleic acid-binding domain different from that of mammals. *Endocrinology* 136, 3774–3783.
- Eberle, A.N., 1988. The Melanotropins. Chemistry, Physiology and Mechanisms of Action. Karger, Basel.
- Edwards, C.K., Ghiasuddin, S.M., Yunger, L.M., Lorence, R.M., Arkins, D., Dantzer, R., Kelley, K.W., 1992. In vivo administration of recombinant growth hormone or gamma interferon activates macrophages: enhanced resistance to experimental *Salmonella typhimurium* infection is correlated with generation of reactive oxygen intermediates. *Infect. Immun.* 60, 2514–2521.
- Ellsaesser, C.F., Clem, L.W., 1986. Haematological and immunological changes in channel catfish stressed by handling and transport. *J. Fish Biol.* 28, 511–521.
- Epselid, S., Løkken, G.B., Steiro, K., Bøggwald, J., 1996. Effects of cortisol and stress on the immune system in Atlantic salmon (*Salmo salar* L.). *Fish Shellfish Immunol.* 6, 95–110.
- Gilchrist, B.J., Tipping, D.R., Levy, A., Baker, B.I., 1999. The influence of acute or chronic stress of different durations on MCH mRNA abundance in rainbow trout (*Oncorhynchus mykiss*). In: Roubos, E.W., Wendelaar Bonga, S.E., Vaudry, H., De Loof, A. (Eds.), Recent Developments in Comparative Endocrinology and Neurobiology. Shaker, Maastricht, pp. 135–139.
- Gonzalez, M.I., Baker, B.I., Wilson, C.A., 1997. Stimulatory effect of melanin-concentrating hormone on luteinising hormone release. *Neuroendocrinology* 66, 254–262.
- Gonzalez, M.I., Vaziri, S., Wilson, C.A., 1996. Behavioural effects of α -MSH and MCH after central administration in the female rat. *Peptides* 17, 171–177.
- Grimm, A.S., 1985. Suppression by cortisol of the mitogen-induced proliferation of peripheral blood leucocytes from plaice, *Pleuronectes platessa* L. In: Manning, M.J., Tatner, M.F. (Eds.), Fish Immunology. Academic Press, London, pp. 236–271.
- Gröneveld, D., Balm, P.H.M., Wendelaar-Bonga, S.E., 1995. Biphasic effect of MCH on α -MSH release from the tilapia (*Oreochromis mossambicus*) pituitary. *Peptides* 16, 945–949.
- Hagi, K., Uno, K., Inaba, K., Muramatsu, S., 1994. Augmenting effect of opioid peptides on murine macrophage activation. *J. Neuroimmunol.* 50, 71–76.
- Harris, J., Bird, D.J., 1997. The effects of α -MSH and MCH on the proliferation of rainbow trout (*Oncorhynchus mykiss*) lymphocytes in vitro. In: Kawashima, S., Kikuyama, S. (Eds.), Advances in Comparative Endocrinology. Monduzzi Editore, Bologna, pp. 1023–1026.
- Harris, J., Bird, D.J., 1998. Alpha-melanocyte stimulating hormone (α -MSH) and melanin-concentrating hormone (MCH) stimulate phagocytosis by head kidney leucocytes of rainbow trout (*Oncorhynchus mykiss*) in vitro. *Fish Shellfish Immunol.* 8, 631–638.
- Harris, J., Bird, D.J., 1999. Effects of melanin-concentrating hormone and α -melanocyte-stimulating hormone on immune responses in rainbow trout (*Oncorhynchus mykiss*). In: Roubos, E.W., Wendelaar Bonga, S.E., Vaudry, H., De Loof, A. (Eds.), Recent Developments in Comparative Endocrinology and Neurobiology. Shaker, Maastricht, pp. 343–345.
- Harris, J., Bird, D.J., 2000. Supernatants from leucocytes treated with melanin-concentrating hormone (MCH) and α -melanocyte stimulating hormone (α -MSH) have a stimulatory effect on rainbow trout (*Oncorhynchus mykiss*) head kidney phagocytes in vitro. *Vet. Immunol. Immunopathol.* In press.
- Harris, J., Bird, D.J., Yeatman, L.A., 1998. Melanin-concentrating hormone (MCH) stimulates the activity of rainbow trout (*Oncorhynchus mykiss*) head kidney phagocytes in vitro. *Fish Shellfish Immunol.* 8, 639–642.
- Hotakainen, P.K., Serlachius, E.M., Lintula, S.I., Alfthan, H.V., Schröder, J.P., Stenman, U.-H.E., 2000. Expression of luteinising hormone and chorionic gonadotropin beta-subunit messenger-RNA and protein in human peripheral blood leukocytes. *Mol. Cell. Endocrinol.* 162, 79–85.

- Hu, S.K., Mitcho, Y.L., Rath, N.C., 1988. Effect of estradiol on interleukin 1 synthesis by macrophages. *Int. J. Immunopharmacol.* 10, 247–252.
- Iida, T., Takahashi, K., Wakabayashi, H., 1989. Decrease in the bacterial activity of normal serum during the spawning period of rainbow trout. *Bull. Jpn. Soc., Sci. Fish* 55, 463–465.
- Jessop, D.S., Jukes, K.E., Lightman, S.L., 1994. Release of α -melanocyte-stimulating hormone from rat splenocytes in vitro is dependent on protein synthesis. *Immunol. Lett.* 41, 191–194.
- Kajita, Y., Sakai, M., Kobayashi, M., Kawauchi, H., 1992. Enhancement of non-specific cytotoxic activity of leucocytes in rainbow trout *Oncorhynchus mykiss* injected with growth hormone. *Fish Shellfish Immunol.* 2, 155–157.
- Kime, D.E., 1987. The steroids. In: Chester-Jones, I., Ingleton, P., Phillips, J.G. (Eds.), *Fundamentals of Comparative Vertebrate Endocrinology*. Plenum Press, New York, pp. 3–56.
- Kitlen, J.W., Hejbøl, E.K., Zinck, T., Varming, K., Byatt, J.C., McLean, E., 1997. Growth performance and respiratory burst activity in rainbow trout treated with growth hormone and vaccine. *Fish Shellfish Immunol.* 7, 297–304.
- Leumbo, P.M., Grazzini, E., Cao, J., Hubatsch, D.A., Pelletier, M., Hoffert, C., St-Onge, S., Pou, C., Labrecque, J., Groblewski, T., O'Donnell, D., Payza, K., Ahmad, S., Walker, P., 1999. The receptor for the orexigenic peptide melanin-concentrating hormone is a G-protein-coupled receptor. *Nature Cell Biol.* 1, 267–271.
- Lipton, J.M., Catania, A., 1997. Anti-inflammatory actions of the neuroimmunomodulator α -MSH. *Immunol. Today* 18, 140–145.
- Ludwig, D.S., Mountjoy, K.G., Tatro, J.B., Gillette, J.A., Frederich, R.C., Flier, J.S., Maratos-Flier, E., 1998. Melanin-concentrating hormone: a functional melanocortin antagonist in the hypothalamus. *Am. J. Physiol.* 274, E627–E633.
- Marc, A.M., Quentel, C., Severe, A., Le Bail, P.Y., Boeuf, G., 1995. Changes in some endocrinological and non-specific immunological parameters during seawater exposure in the brown trout. *J. Fish Biol.* 46, 1065–1081.
- Maule, A.G., Schreck, C.B., 1990a. Changes in numbers of leukocytes in immune organs of juvenile coho salmon after acute stress or cortisol treatment. *J. Aquat. Anim. Health* 2, 298–304.
- Maule, A.G., Schreck, C.B., 1990b. Glucocorticoid receptors in leukocytes and gill of juvenile coho salmon (*Oncorhynchus kisutch*). *Gen. Comp. Endocrinol.* 77, 448–455.
- Maule, A.G., Schrock, R., Slater, C., Fitzpatrick, M.S., Schreck, C.B., 1996. Immune and endocrine responses of adult chinook salmon during freshwater immigration and sexual maturation. *Fish Shellfish Immunol.* 6, 221–223.
- Maule, A.G., Tripp, R.A., Kaattari, S.L., Schreck, C.B., 1989. Stress alters immune function and disease resistance in chinook salmon (*Oncorhynchus tshawytscha*). *J. Endocrinol.* 120, 135–142.
- McLeay, D.J., 1973a. Effects of ACTH on the pituitary-interrenal axis and abundance of white blood cell types in juvenile coho salmon, *Oncorhynchus kisutch*. *Gen. Comp. Endocrinol.* 21, 431–440.
- McLeay, D.J., 1973b. Effects of cortisol and dexamethasone on the pituitary-interrenal axis and abundance of white blood cell types in juvenile coho salmon, *Oncorhynchus kisutch*. *Gen. Comp. Endocrinol.* 21, 441–450.
- Miller, C., Hrubby, V.J., Matsunaga, T.O., Bickford, P.C., 1993. Alpha-MSH and MCH are functional antagonists in a CNS auditory gating paradigm. *Peptides* 14, 431–440.
- Muñoz, P., Calduch-Giner, J.A., Sitjà-Bobadilla, A., Alvarez-Pellitero, P., Pérez-Sánchez, J., 1998. Modulation of the respiratory burst activity of Mediterranean sea bass (*Dicentrarchus labrax* L.) phagocytes by growth hormone and parasitic status. *Fish Shellfish Immunol.* 8, 25–36.
- Murphy, W.J., Longo, D.L., 2000. Growth hormone as an immunomodulating therapeutic agent. *Immunol. Today* 121, 211–213.
- Nagae, M., Fuda, H., Ura, K., Kawamura, H., Adachi, S., Hara, A., Yamauchi, K., 1994. The effect of cortisol administration on blood plasma immunoglobulin M (IgM) concentrations in masu salmon (*Oncorhynchus masou*). *Fish Physiol. Biochem.* 13, 41–48.
- Nahon, J.-L., Presse, F., Breton, C., Hervieu, G., Schorpp, M., 1993. Structure and regulation of the melanin-concentrating hormone gene. *Ann. NY Acad. Sci.* 680, 111–129.
- Narnaware, Y.K., Baker, B.I., 1996. Evidence that cortisol may protect against the immediate effects of stress on circulating leucocytes in the trout. *Gen. Comp. Endocrinol.* 103, 359–366.

- Narnaware, Y.K., Baker, B.I., Tomlinson, M.G., 1994. The effect of various stresses, corticosteroids and adrenergic agents on phagocytosis in the rainbow trout *Oncorhynchus mykiss*. *Fish Physiol. Biochem.* 13, 31–40.
- Narnaware, Y.K., Kelly, S.P., Woo, N.Y.S., 1997. Effect of injected growth hormone on phagocytosis in silver sea bream (*Sparus sarba*) adapted to hyper- and hypo-osmotic salinities. *Fish Shellfish Immunol.* 7, 515–517.
- Narnaware, Y.K., Kelly, S.P., Woo, N.Y.S., 1998. Stimulation of macrophage phagocytosis and lymphocyte count by exogenous prolactin administration in silver sea bream (*Sparus sarba*) adapted to hyper- and hypo-osmotic salinities. *Vet. Immunol. Immunopathol.* 61, 389–393.
- Ortega, E., Forner, M.A., Barriga, C., 1996. Effect of prolactin on the in vitro phagocytic capacity of macrophages. *Comp. Immunol. Microbiol. Infect. Dis.* 19, 139–146.
- Ottaviani, E., Franchini, A., Francheschi, C., 1995. Evidence for the presence of immunoreactive POMC-derived peptides and cytokines in the thymus of the goldfish (*Carassius c. auratus*). *Histochem. J.* 27, 597–601.
- Patino, R., Maule, A.G., 1997. Estrogen receptors in leukocytes from immature channel catfish. *Dev. Comp. Immunol.* 21, 123.
- Pickering, A.D., 1984. Cortisol-induced lymphocytopenia in brown trout, *Salmo trutta* L. *Freshwater Biol.* 21, 47–55.
- Pickering, A.D., Christie, P., 1980. Sexual differences in the incidence and severity of ectoparasitic infestation of the brown trout, *Salmo trutta*. L. *J. Fish Biol.* 16, 669–683.
- Pickering, A.D., Pottinger, T.G., 1989. Stress responses and disease resistance in salmonid fish: effects of chronic elevation of plasma cortisol. *Fish Physiol. Biochem.* 7, 253–258.
- Plotnikoff, N.P., Faith, R.E., Murgo, A.J., Herberman, R.B., Good, R.A., 1997. Methionine enkephalin: a new cytokine-human studies. *Clin. Immunol. Immunopathol.* 82, 93–101.
- Prunet, P., Boeuf, G., Bolton, J.P., Young, G., 1989. Smoltification and seawater adaptation in Atlantic salmon (*Salmo salar*): plasma prolactin, growth hormone and thyroid hormones. *Gen. Comp. Endocrinol.* 74, 355–364.
- Pulsford, A.L., Crampe, M., Langston, A., Glynn, P.J., 1995. Modulatory effects of disease, stress, copper, TBT and Vitamin E on the immune system of flatfish. *Fish Shellfish Immunol.* 5, 631–643.
- Pulsford, A.L., Lemaire-Gony, S., Tomlinson, M., Collingwood, N., Glynn, P.J., 1994. Effects of acute stress on the immune system of the dab, *Limanda limanda*. *Comp. Biochem. Physiol.* 109C, 129–139.
- Rajora, N., Ceriani, G., Catania, A., Star, R.A., Murphy, M.T., Lipton, J.M., 1996. α -MSH production, receptors, and influence on neopterin in a human monocyte/macrophage cell line. *J. Leukoc. Biol.* 59, 248–253.
- Rance, T.A., Baker, B.I., 1979. The teleost melanin-concentrating hormone—a pituitary hormone of hypothalamic origin. *Gen. Comp. Endocrinol.* 37, 64–73.
- Ridgeway, G.J., 1962. Demonstration of blood types in rainbow trout and salmon by isoimmunisation. *Ann. NY Acad. Sci.* 97, 111–118.
- Ruglys, M.P., 1985. The secondary immune response of young carp, *Cyprinus carpio* L., following injection of cortisol. *J. Fish Biol.* 26, 429–434.
- Saito, Y., Nothacker, H.P., Wang, Z., Lin, S.H.-S., Leslie, F., Civelli, O., 1999. Molecular characterization of the melanin-concentrating-hormone receptor. *Nature* 400, 265–269.
- Sakai, M., Kobayashi, M., Kawauchi, H., 1995. Enhancement of chemiluminescent responses of phagocytic cells from rainbow trout, *Oncorhynchus mykiss*, by injection of growth hormone. *Fish Shellfish Immunol.* 5, 375–379.
- Sakai, M., Kajita, Y., Kobayashi, M., Kawauchi, H., 1996a. Increase in haemolytic activity of serum from rainbow trout *Oncorhynchus mykiss* injected with exogenous growth hormone. *Fish Shellfish Immunol.* 6, 615–617.
- Sakai, M., Kajita, Y., Kobayashi, M., Kawauchi, H., 1997. Immunostimulating effect of growth hormone: in vivo administration of growth hormone in rainbow trout enhances resistance to *Vibrio anguillarum* infection. *Vet. Immunol. Immunopathol.* 57, 1–6.
- Sakai, M., Kobayashi, M., Kawauchi, H., 1996b. Mitogenic effect of growth hormone and prolactin on chum salmon *Oncorhynchus keta* leukocytes in vitro. *Vet. Immunol. Immunopathol.* 53, 185–189.
- Sakai, M., Kobayashi, M., Kawauchi, H., 1996c. In vitro activation of fish phagocytic cells by GH, prolactin and somatolactin. *J. Endocrinol.* 151, 113–118.

- Schreck, C.B., 1996. Immunomodulation: endogenous factors. In: Iwama, G., Nakanishi, T. (Eds.), *The Fish Immune System: Organism, Pathogen and Environment*. Academic Press, London, pp. 311–337.
- Schreiber, A.D., Netti, F.M., Sanders, M.C., King, M., Szabolcs, P., Friedman, D., Gomez, F., 1988. Effect of endogenous and synthetic sex steroids on the clearance of antibody-coated cells. *J. Immunol.* 141, 2959–2966.
- Scott, A.P., 1987. Reproductive endocrinology of fish. In: Chester-Jones, I., Ingleton, P., Phillips, J.G. (Eds.), *Fundamentals of Comparative Vertebrate Endocrinology*. Plenum Press, New York, pp. 223–256.
- Seaman, W.E., Blackman, M.A., Gindhart, T.D., Roubinian, J.R., Loeb, J.M., Talal, N., 1978. β -estradiol reduces natural killer cells in mice. *J. Immunol.* 121, 2193–2198.
- Sharp, B.M., Keane, W.F., Suh, W.J., Gekker, G., Tsukayama, D.T., Peterson, P.K., 1985. Opioid peptides rapidly stimulate superoxide production by human polymorphonuclear leukocytes and macrophages. *Endocrinology* 117, 793–795.
- Shih, S.T., Khorram, O., Lipton, J.M., McCann, S.M., 1986. Central administration of α -MSH antiserum augments fever in the rabbit. *Am. J. Physiol.* 250, R803–R806.
- Shimomura, Y., Mori, M., Sugo, T., Ishibashi, Y., Abe, M., Kurokawa, T., Onda, H., Nishimura, O., Sumino, Y., Fujino, M., 1999. Isolation and identification of melanin-concentrating hormone as the endogenous ligand of the SLC-1 receptor. *Biochem. Biophys. Res. Comm.* 261, 622–626.
- Slater, C.H., Schreck, C.B., 1993. Testosterone alters the immune response of chinook salmon, *Oncorhynchus tshawytscha*. *Gen. Comp. Endocrinol.* 89, 291–298.
- Slater, C.H., Schreck, C.B., 1997. Physiological levels of testosterone kill salmonid leukocytes in vitro. *Gen. Comp. Endocrinol.* 106, 113–119.
- Slater, C.H., Fitzpatrick, M.S., Schreck, C.B., 1995. Characterization of an androgen receptor in salmonid lymphocytes: possible link to androgen induced immunosuppression. *Gen. Comp. Endocrinol.* 100, 218–225.
- Sprang, S.R., Bazan, J.F., 1993. Cytokine structural taxonomy and mechanisms of receptor engagement. *Curr. Opin. Struc. Biol.* 3, 815–827.
- Star, R.A., Rajora, N., Huang, J., Stock, R.C., Catania, A., Lipton, J.M., 1995. Evidence of autocrine modulation of macrophage nitric oxide synthase by α -melanocyte-stimulating hormone. *Proc. Natl. Acad. Sci. U.S.A.* 92, 8016–8020.
- Stein, M., Miller, A.H., 1993. Stress, the hypothalamic-pituitary-adrenal axis, and immune function. *Adv. Exp. Med. Biol.* 335, 1–5.
- Sternberg, E.M., Chrousos, G.P., Wilder, R.L., Gold, P.W., 1992. The stress response and the regulation of inflammatory disease. *Ann. Int. Med.* 117, 854–866.
- Sthoeger, Z.M., Chiorazzi, N., Lahita, R.G., 1988. Regulation of the immune response by sex hormones. I. In vitro effects of estradiol and testosterone on pokeweed mitogen-induced human B cell differentiation. *J. Immunol.* 141, 91–98.
- Stefano, G.B., Salzet, M., 1999. Invertebrate opioid precursors: evolutionary conservation and the significance of enzymatic processing. *Int. Rev. Cytol.* 187, 261–286.
- Sumner, F.B., Doudoroff, P., 1938. The effects of light and dark backgrounds upon the incidence of a seemingly infectious disease in fishes. *Proc. Natl. Acad. Sci. U.S.A.* 24, 463–466.
- Takahashi, A., Amemiya, Y., Sakai, M., Yasuda, A., Suzuki, N., Sasayama, Y., Kawauchi, H., 1999. Occurrence of four MSHs in dogfish POMC and their immunomodulating effects. *Ann. NY Acad. Sci.* 885, 459–463.
- Takahashi, A., Takasaka, T., Yasuda, A., Amemiya, Y., Sakai, M., Kawauchi, H., 2000. Identification of carp proopiomelanocortin-related peptides and their effects on phagocytes. *Fish Shellfish Immunol.* 10, 273–284.
- Taylor, A.W., Streilein, J.W., Cousins, S.W., 1992. Identification of alpha-melanocyte stimulating hormone as a potential immunosuppressive factor in aqueous humor. *Curr. Eye Res.* 11, 1199–1206.
- Tripp, R.A., Maule, A.G., Schreck, C.B., Kaattari, S.L., 1987. Cortisol mediated suppression of salmonid lymphocyte responses in vitro. *Dev. Comp. Immunol.* 11, 565–576.
- Van Epps, D.E., Saland, L., 1984. β -endorphin and met-enkephalin stimulate human peripheral blood mononuclear cells chemotaxis. *J. Immunol.* 132, 3046–3053.
- Verburg-van Kemenade, B.M.L., Nowak, B., Engelsma, M.Y., Weyts, F.A.A., 1999. Differential effects of cortisol on apoptosis and proliferation of carp B-lymphocytes from head kidney, spleen and blood. *Fish Shellfish Immunol.* 9, 405–415.

- Warwick-Davies, J., Lowrie, D.B., Cole, P.J., 1995. Growth hormone is a human macrophage activating factor-priming of human monocytes for enhanced release of H₂O₂. *J. Immunol.* 154, 1909–1918.
- Watanabe, T., Hiltz, M., Catania, A., Lipton, J.M., 1993. Inhibition of IL-1 β -induced peripheral inflammation by peripheral and central administration of analogs of the neuropeptide α -MSH. *Brain Res. Bull.* 32, 311–314.
- Watanuki, H., Gushiken, Y., Takahashi, A., Yasuda, A., Sakai, M., 2000. In vitro modulation of fish phagocytic cells by β -endorphin. *Fish Shellfish Immunol.* 10, 203–212.
- Watanuki, N., Takahashi, A., Yasuda, A., Sakai, M., 1999. Kidney leucocytes of rainbow trout, *Oncorhynchus mykiss*, are activated by intraperitoneal injection of β -endorphin. *Vet. Immunol. Immunopathol.* 71, 89–97.
- Weyts, F.A.A., Cohen, N., Flik, G., Verburg-van Kemenade, B.M.L., 1999. Interactions between the immune and endocrine system and the hypothalamo-pituitary-interrenal axis in fish. *Fish Shellfish Immunol.* 9, 1–20.
- Weyts, F.A.A., Flik, G., Rombout, J.H.W.M., Verburg-van Kemenade, B.M.L., 1998a. Cortisol induces apoptosis in activated B cells, not in other lymphoid cells of the common carp, *Cyprinus carpio* L. *Dev. Comp. Immunol.* 22, 551–562.
- Weyts, F.A.A., Verburg-van Kemenade, B.M.L., Flik, G., Lambert, J.G.D., Wendelaar Bonga, S.E., 1997. Conservation of apoptosis as an immune regulatory mechanism: effects of cortisol and cortisone on carp lymphocytes. *Brain Behav. Immun.* 11, 95–105.
- Weyts, F.A.A., Verburg-van Kemenade, B.M.L., Flik, G., 1998b. Characterisation of glucocorticoid receptors in peripheral blood leukocytes of carp, *Cyprinus carpio* L. *Gen. Comp. Endocrinol.* 111, 1–8.
- Wiik, R., Andersen, K., Uglenes, I., Egidius, E., 1989. Cortisol-induced increase in susceptibility of Atlantic salmon, *Salmo salar*, to *Vibrio salmonicida*, together with effects on the blood cell pattern. *Aquaculture* 83, 201–215.
- Wyle, F.A., Kent, J.R., 1977. Immunosuppression by sex steroid hormones. I. The effect upon PHA- and PPD-stimulated lymphocytes. *Clin. Exp. Immunol.* 27, 407–415.
- Yada, T., Nagae, M., Moriyama, S., Azuma, T., 1999. Effects of prolactin and growth hormone on plasma immunoglobulin M levels of hypophysectomized rainbow trout, *Oncorhynchus mykiss*. *Gen. Comp. Endocrinol.* 115, 46–52.