



A review of the multifunctional hormone melatonin and a new hypothesis involving osmoregulation

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Abstract

The pineal hormone melatonin is a potent regulator of seasonal and circadian rhythms in vertebrates, among them fish. Melatonin synthesis shows a diurnal rhythm with higher levels at night. In recent years, the pineal gland and its major product gained a number of attributes suggesting their role in integration of various neural and endocrine functions. Besides the well-established physiological effects mediated via high-affinity cell membrane receptors belonging to the superfamily of G-protein – coupled receptors, melatonin reveals direct intracellular actions.

This paper attempts to synthesise the physiological roles of this multifaceted hormone in fish. The use of higher vertebrates paradigms (considering every limit in interpretation) was essential due to lack of satisfactory data on fish. The actions of melatonin in major organs responsible for osmoregulation in fish are discussed. The influence of melatonin on water/ion excretion by affecting the circulatory blood hemodynamic and by interrelations with other hormones systems engaged in water/ion homeostasis are considered. New data providing the first evidence for the presence of melatonin binding sites in fish gills and kidneys are presented. The paper suggests a new approach that may lead to an improved understanding of osmoregulation processes.

One hormone – numerous effects

Melatonin (N-acetyl-5methoxytryptamine) came to scientific attention as a potent agent for blanching in

frog skins in the late 1950s (Lerner et al., 1958). The indole hormone is primarily synthesised and secreted by the pineal gland in all classes of vertebrate. In all species examined, melatonin production

and release is low during the light period and rises during the dark period (Binkley, 1988; Bolliet et al., 1996a). Melatonin is not stored in the pineal, so its plasma concentration reflects the synthesis capacity of the gland. The past decades have seen a flood of information on the metabolic and physiological effects of melatonin in vertebrates, especially in mammals (Binkley, 1988; Reiter, 1995). Observations indicate that melatonin as a signal of photoperiod regulates an unusual number of biological phenomena, including reproduction, day/night activity, sleep behaviour and many other physiological events associated with daily or seasonal rhythms (Reiter, 1993, 1995; Arendt, 1998). However, it appears, that melatonin's primary function may relate not only to photoperiodism, but also to its antioxidative role (Reiter et al., 1996). Melatonin has been found to be highly effective preventive antioxidant and free radical scavenger protecting organism from oxidative damage (Reiter et al., 2000). Moreover, melatonin has gained considerable public interest as a 'wonder drug' in humans against ageing, insomnia, jet lag, immune dysfunction, and cancer (Bartsch et al., 1992; Reiter, 1995; Liebmann et al., 1997; Arendt, 1998), but its actual value as a medicament is not universally supported (Webb and Pulg-Domingo, 1995).

Many of the established physiological effects of melatonin are mediated via high-affinity cell membrane receptors. The use of the melatonin agonist, 2-[¹²⁵I]iodomelatonin, has provided the exact localization of receptors (Stankov et al., 1993). High-affinity 2-[¹²⁵I]iodomelatonin binding sites were detected not only in the central nervous system (CNS), but also in several peripheral mammalian and avian tissues, such as lymphocytes, caudal artery, Harderian gland, adrenal gland, spleen, gut, gonads and kidney (Stankov et al., 1993). These high-affinity melatonin receptors belong to the superfamily of guanine nucleotide binding protein (G-protein) – coupled receptors (Niles, 1997; Reppert, 1997). Cloning of several G-protein-coupled melatonin receptor genes has revealed that three melatonin receptor subtypes exist (Reppert, 1997).

Until recently, much of what was known about the functions of melatonin came from its presumed interactions with membrane-bound receptors on cells in specific areas of the brain and peripheral tissues (Stankov et al., 1993; Niles, 1997). It was recently discovered that melatonin also has intracellular activity. Owing to its high lipid and aqueous solubility the hormone can enter cells readily and affect

processes that do not require its interactions with receptors, i.e., as a free radical scavenger and antioxidant (Reiter et al., 2000). Furthermore, the nuclear melatonin binding sites were identified and characterised in many cells and the interactions of melatonin with its nuclear and membrane receptors have been considered in terms of regulating gene expression (Reiter et al., 1996). The variety of melatonin sites of action in cells may explain the enormous variability of melatonin effects in organisms.

The objective of this paper is to synthesise the physiological roles of melatonin, especially in fish, and to put them into the context of the osmoregulatory process, which is of vital importance to this vertebrate class.

Melatonin in fish – physiological approach

Fish studies on physiological effects of melatonin are lagging far behind mammalian and avian studies. Circadian changes in skin darkness in teleosts drew attention to melatonin as a possible factor responsible for pigment aggregation in melanophores (Reed, 1968). The majority of current investigations concentrate on the influence of photoperiod and temperature on melatonin synthesis capacity and tend to correlate the diurnal or seasonal changes in fish organism with melatonin (Max and Menaker, 1992; Meissl and Brandstätter, 1992; Zachmann et al., 1992b; Falcon et al., 1994; Bolliet et al., 1996a; Mayer et al., 1997). Generally, the role of the hormone in the mechanism controlling rhythmic adaptations to daily and seasonal cycles in fish is well accepted. Studies in a few teleost species such as goldfish (*Carassius auratus*), white sucker (*Catostomus commersoni*), pike (*Esox lucius*), zebrafish (*Danio rerio*) and gilthead bream (*Sparus aurata*) suggest the presence of cellular circadian oscillators within the pineal organ (Iigo et al., 1991; Zachmann et al., 1992b; Bolliet et al., 1996b; Cahill, 1996; Molina-Borja et al., 1996). Only the pineal of rainbow trout (*Oncorhynchus mykiss*), brown trout (*Salmo trutta*) and common dentex (*Dentex dentex*) do not appear to contain a circadian oscillator. In these species melatonin synthesis is directly controlled by the pattern of illumination (Gern and Greenhouse, 1988; Max and Menaker, 1992; Pavlidis et al., 1999). The annual pattern of melatonin synthesis, i.e., a short period of high synthesis in summer and prolonged period of high synthesis in winter, plays the role of "endocrine calendar" in the organism and synchron-

ises the reproductive cycles with cycles in the environment (Reiter, 1993).

Thus, it can be expected, that melatonin related to circadian and circannual rhythmicity may be implicated in a wide spectrum of physiological and behavioural events, such as gonadal maturation and spawning, parr-smolt transformation in salmonids, migration behaviour etc. (Popek et al., 1992; Zachmann et al., 1992a; Mayer et al., 1997; Amano et al., 2000). The time of migration is precisely defined in every species. The mediation of seasonal environmental changes of light and temperature in the organism is assumed to be linked to melatonin, and further, to its interrelation with other hormones. As expected, migrations demand extensive osmoregulatory adjustments and implicate significant physiological changes in fish (Bentley, 1971; Boeuf, 1993). Consequently, some hormonal interactions in fish have been postulated (Kulczykowska, 1995).

Melatonin – a new factor contributing to osmoregulation in terrestrial vertebrates?

Several organs are involved in osmoregulation: kidney, gill, gastrointestinal tract, skin, urinary bladder, but their relative importance varies in aquatic and terrestrial species. Terrestrial vertebrates are equipped with kidneys, which are highly specialised in preserving water and ions. In fish, however, the gills are the main site for direct osmoregulation, and the role of the kidney is reduced.

Several lines of evidence indicate that melatonin may affect the water budget in higher vertebrates. The presence of 2-[¹²⁵I]iodomelatonin binding sites in the kidney of several mammalian and avian species suggests the possibility of a direct action of melatonin on the renal system (Richardson et al., 1992; Song and Pang, 1992; Song et al., 1993, 1995, 1996). A regional distribution study in the male guinea pig kidney showed that specific binding of 2-[¹²⁵I]iodomelatonin was 8-fold higher in the cortical region, which contains renal corpuscles, than that in the medullary region (Song et al., 1993). Similar binding of this ligand was observed in the human kidney (Song et al., 1995). Song et al. (1997) provided the first direct evidence that the melatonin receptors Mel_{1a} in rabbits are localized to the basolateral membrane of the renal cortical epithelium, especially the early proximal tubule. This localization strongly suggests that the

proximal tubule plays a significant role in mediating the renal action of melatonin in some mammals.

The general assumption is that the presence of high-affinity membrane receptors of a hormone supports its action at this site. Although the peripheral effects of melatonin were mainly mediated through the interaction of hormone with its specific membrane receptors (Stankov et al., 1993), the additional direct intracellular action of melatonin in non-neural tissues cannot be excluded. A few reports concerned with the impact of the pineal gland and melatonin on electrolyte and water metabolism provide interesting findings. It is known that in humans nocturnal excretion rates of Na⁺, Cl⁻ and K⁺ are only 50% of the observed excretion rate during the day (Koopman et al., 1989). Administration of melatonin to Syrian hamsters (*Mesocricetus auratus*) decreases urinary sodium and potassium concentrations as well as urine osmolality (Richardson et al., 1992). Barbarossa et al. (1960) demonstrated that removal of the pineal reduces renal water excretion, which is reversed upon administration of pineal extracts. Morton (1990) reported on the influence of light on plasma cation levels in rats and proposed the presence of regulatory mechanisms between melatonin and cations. Seasonal studies performed in elderly human subjects suggested a possible interrelation between melatonin and serum osmolality (Asplund et al., 1998). Moreover, the decrease of glomerular filtration rate (GFR) observed in parallel with an increase of plasma melatonin in ewes suggested the importance of melatonin in regulation of GFR (Tsuda et al., 1995).

It can be expected, however, that the relationship between melatonin and systems controlling fluid balance is more complex and probably exceeds the direct action of the hormone on kidneys. The changes in urine production may be a result of the increase in water consumption and/or water excretion, and suggest a central action of melatonin affecting vasopressin (AVP) secretion and/or thirst mechanism. On the other hand, melatonin may affect the circulating and/or intrarenal renin-angiotensin system in mammalian vertebrates. Pinealectomy was found to induce hypertension and elevated daily urine production with decreased potassium and sodium contents in rats. The effects were postulated to involve the renin-angiotensin system with elevated plasma renin activity detected in pinealectomized rats (Karppanen et al., 1975; Acuna et al., 1984). Melatonin treatment is known to decrease plasma renin concentration and

reduce blood pressure in spontaneously hypertensive rats (Kawashima et al., 1987).

Thus, taken together, studies in terrestrial animals provide evidence that melatonin may contribute to body fluid regulation and provide the hypothetical premise that this may be true for other vertebrate class, i.e., fish.

Melatonin – a factor contributing to osmoregulation in fish?

Homeostatic responses of fish to osmotic perturbation are illustrated in Figure 1. The mechanisms include components relating to water balance and electrolytes balance. Although the biological structures and regulatory mechanisms participating in osmoregulation in various vertebrates are different, they also have many common features. Applying the mammalian or avian paradigms in order to explore the fish situation is useful within certain limits. Generally, fishes possess less complicated mechanism for regulation of salt and water balance, because of easier access to these elements in water. Fish are immersed in solutions with a wide range of osmotic concentration. However, water and ions in fish are regulated in the opposite direction in freshwater and seawater, and many fishes use both during a lifetime, i.e., anadromous salmon etc. The strategies used in the maintenance of solute balance follow a general rule where marine fish must secrete NaCl and conserve water and freshwater fish must accumulate salt from environment and eliminate excess water.

The questions arise:

- Does melatonin play a role in osmoregulation in fish?
- How are the physiological systems of the fish responsible for osmoregulation, which are potential goals for melatonin action?

The most important organs for osmoregulation in fish are the gills, gastrointestinal tract and the kidney. Osmoregulatory tissues possess a high level of membrane-bound enzyme sodium ion-potassium ion-adenosinetriphosphatase activity i.e., Na⁺-K⁺-ATPase, “sodium pump”. Diel changes in plasma monovalent ion concentration were observed in various fish species: common dentex, sea bream (*Sparus aurata*), sea bass (*Dicentrarchus labrax*), carp (*Cyprinus carpio*) and rainbow trout (Carillo et al., 1986; Kühn et al., 1986; Laidley and Leatherland, 1988; Pavlidis et al., 1997). Seasonal vari-

ations in plasma Na⁺, Cl⁻ and osmolality were observed in Atlantic cod (*Gadus morhua*) and American plaice (*Hippoglossoides platessoides*; Audet et al., 1993). The daily and seasonal changes in plasma ion concentration reflect variations in ion exchange across the gut and gill epithelia and/or changes in urinary electrolyte excretion and may suggest melatonin involvement. Furthermore, higher values of Na⁺ and Cl⁻ paralleling high melatonin plasma levels were reported in coho salmon (*Oncorhynchus kisutch*) during seawater adaptation (Folmar and Dickhoff, 1981) and in common dentex (Pavlidis et al., 1999). It was suggested that observed increases in plasma melatonin levels during entry of coho salmon into seawater is a part of an endocrine adjustment facilitating osmoregulation (Gern et al., 1984). As was reported in rainbow trout, plasma melatonin concentration in brackish water adapted fish was significantly higher than that in fresh water animals (Kulczykowska, 1999). The physiological significance of these observations is difficult to assess at present, but may suggest the role of melatonin in osmotic adaptation mechanism. The role of potential interaction between melatonin and arginine vasotocin (AVT), hypothalamo-neurohypophysial osmoregulatory hormone in fish, has been postulated (Kulczykowska, 1995 and 1998; Kulczykowska et al., 2001), but clinical trials remain to be done.

Gill

The gill is the primary site of active ion transport responsible for body electrolyte homeostasis in teleosts. In freshwater teleosts the gills actively absorb salt, whereas seawater teleosts actively excrete NaCl. The branchial chloride cells play an essential role in the seawater acclimation of euryhaline teleost. They are equipped with high levels of activity in Na⁺-K⁺-ATPase, an important enzyme in ionosmotic regulation responsible for Cl⁻ secretion. Interestingly, the activity of gill Na⁺-K⁺ – ATPase shows seasonal changes in Arctic char (*Salvelinus alpinus*; Staurnes, 1993).

Unfortunately, to my knowledge, there are no records on the presence of melatonin receptors in gill tissue or documented melatonin action therein. The absence of the proof is not the proof of absence. Therefore, I undertook studies of ligand 2-[¹²⁵I]iodomelatonin binding sites in the gills of freshwater rainbow trout and seawater flounder (*Platichthys flesus*). The studies summarised below provide the

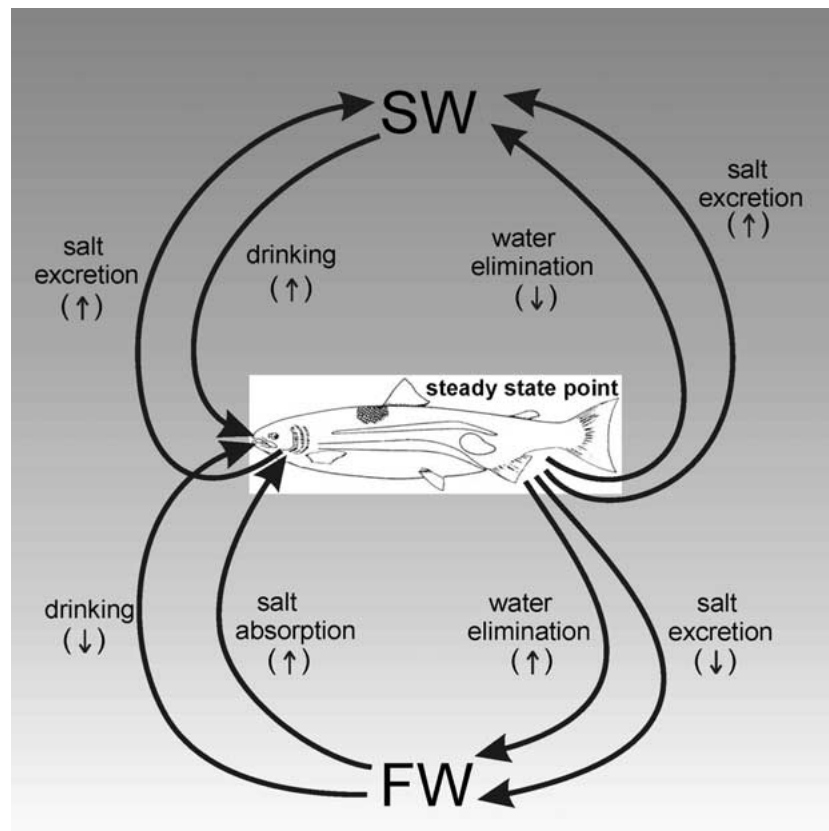


Figure 1. Homeostatic responses of fish to osmotic perturbation. SW – seawater; FW – freshwater.

first evidence for the presence of membrane melatonin binding sites in gills of both fish species.

Gastrointestinal tract

The second important organ for water and salt exchange in fish is the gastrointestinal tract (GIT). The GIT's role differs in various fish species. Fish living in fresh water scarcely drink, because they passively intake water due to the osmotic influx of water through the gills. Conversely, fish in seawater drink constantly. Melatonin was detected by radioimmunoassay (RIA) in all segments (esophagus, stomach, proximal gut and distal gut) of the GIT of several species of fish: sturgeon (*Acipenser fulvescens*), rainbow trout and carp (Bubenik and Pang, 1997). High affinity melatonin binding sites have been identified in the gastrointestinal tract of several vertebrate species including chicken, duck, mouse and human (Martin et al., 1998). Melatonin produced in the gastrointestinal tract probably acts as a paracrine and/or autocrine factor. However, this does not preclude the possi-

bility that the hormone reaches peripheral circulation, and thus, contributes to systemic blood hormone level. Nevertheless, the function of melatonin in the GIT is not yet well understood. Several reports have focused on the role of melatonin as a local regulator of gastrointestinal motility in mammals (Martin et al., 1998), but melatonin has also been shown to inhibit sodium transport in the rat colon (Legris et al., 1982).

The physiological role of melatonin in the GIT of fish is a matter of debate and further studies are needed to fill existing gaps in our knowledge. As was mentioned above, freshwater fish scarcely drink, but the intestine actively transports sodium from the lumen to the blood. Drinking and subsequent absorption of water by the intestine is essential for seawater fish. Fishes migrating from fresh- to seawater start to drink in response to angiotensin II, a potent diuretic hormone, or in direct response to external Cl^- ions (Takei, 2000). As was reported in mammals, melatonin is known to affect their renin-angiotensin system (Karppanen et al., 1975; Acuna et al., 1984; Kawashima et al., 1987). This mechanism could also

be active in fish, although there is no experimental evidence for or against it. Thus, melatonin may influence the mechanism of drinking and consequently the water uptake in gut of euryhaline fish. However, the melatonin paracrine effect on active sodium transport in GIT cannot be excluded. Interestingly, the enzyme $\text{Na}^+\text{-K}^+\text{-ATPase}$ involved in ionosmotic regulation shows preadaptative seasonal changes in trout intestine (Rey et al., 1991).

Kidney

In fish the principal exchange of osmotically important ions and water movement takes place through gills and GIT, however, the role of the kidney in osmoregulation should not be underestimated. Fish are the only vertebrates with kidneys able to produce urine by glomerular and aglomerular mechanisms defined by Beyenbach (1995) and Renfro (1999). Glomeruli appear to be particularly suited to the excretion of the large volumes of water accumulated by fish living in fresh water. The renal tubules of fish are differentiated from one or two tubular segments to the complement structure of the vertebrate nephron. Thus, the contribution of the kidney to extracellular fluid homeostasis is not universal in fish, and renal function spans the whole spectrum from glomerular filtration to tubular secretion. The main function of the proximal tubule of glomerular kidney in higher vertebrates is to reabsorb fluid. Surprisingly, the renal proximal tubules of glomerular kidneys in marine and euryhaline fish (winter flounder (*Pseudopleuronectes americanus*), dogfish shark (*Squalus acanthias*) and killifish (*Fundulus heteroclitus*)) appear to secrete fluids containing Na^+ and Cl^- . Interestingly, the same phenomenon is observed in the kidney of aglomerular toadfish (*Opsanus tau*) (for review see: Beyenbach, 1995; Renfro, 1999).

As was mentioned above, avian and mammalian melatonin binding sites are located in the basolateral membrane of the renal cortical epithelium. This suggests that melatonin may influence the proximal tubular function and can be considered one of the factors responsible for diurnal variations in urine monovalent ions secretion in these vertebrate classes. Unfortunately, to date, there are no equivalent findings available for fish, though, daily and seasonal changes in plasma ions concentration in various fish species are known.

Besides the melatonin influence on electrolyte and water movements in renal tubule the probable effect

on renal hemodynamic should be considered. In many teleost fish, in contrast to mammals, glomerulotubular balance seems to be poorly developed, and GFR is readily increased by an increase in renal perfusion pressure (Nishimura and Bailey, 1982). Therefore, any changes in systemic blood pressure can affect glomerular filtration in fish kidney. It was shown that melatonin can influence the changes in blood pressure (BP) in cod induced by fish neurohypophysial hormone arginine vasotocin (Kulczykowska, 1998). Moreover, melatonin administered in cod at night caused the prolonged BP decrease. My unpublished studies demonstrate that melatonin injected into the circulation in doses considered as physiologically relevant (10 ng/kg) also caused the prolonged and significant decrease in blood pressure in rainbow trout and flounder. Thus, higher plasma melatonin concentrations inducing sustained hypotension may be responsible for a decrease in GFR, and thus, affect the water/ion balance in fish. The hypotensive effect of melatonin and its vascular receptors have been described in mammals (Birau et al., 1981; Kawashima et al., 1987; Viswanathan et al., 1993). Reduced GFR and antidiuresis observed after adaptation of rainbow trout to seawater is considered a part of their physiological adaptation to changed environment (Holmes and McBean, 1963).

Preliminary results: melatonin binding sites in gills and kidneys of rainbow trout and flounder

Rainbow trout and flounder were kept in freshwater and in seawater, respectively, at artificial light-dark cycle 12:12. The kidney and gill samples were dissected and homogenized. Specific binding of ligand 2-[^{125}I]iodomelatonin to homogenates from both tissues membranes were investigated.

Specific binding (SB) was calculated as the difference between total binding and nonspecific binding (not displaced in the presence of 0.5 μM nonlabeled melatonin). SB reached a plateau at approximately 100–120 pM. Melatonin binding sites were saturated at 150 pM. The binding affinities (K_d) and binding densities (B_{max}) were calculated.

My preliminary study provides the first evidence for the presence of melatonin binding sites in fish gills and kidneys. Binding of 2-[^{125}I]iodomelatonin was present in kidneys and gills of both fish species: freshwater rainbow trout and seawater flounder. Values for mean equilibrium dissociation constant K_d , and mean theoretical maximum receptor number B_{max}

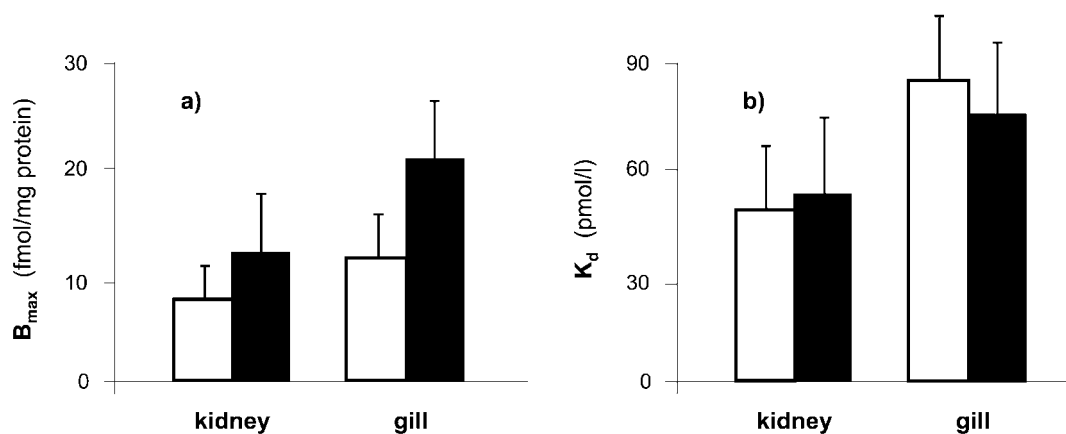


Figure 2. Maximal binding density (B_{max}) and binding affinity (K_d) of 2-[125 I]iodomelatonin binding sites in kidneys and gills of rainbow trout (white bars) and flounder (black bars). Data are the mean \pm SEM; $n = 6$.

ranged between 48–85 pM and 8–22 fmol/mg protein, respectively. The binding sites with K_d values in the picomolar range appear of high affinity. The differences in K_d and B_{max} values are tissue- and species-dependent (Figure 2). The physiological relevance of these variations needs further investigations.

Interactions with other hormones

The fishes possess many endocrine organs engaged in osmoregulation, which are homologous to that of tetrapods. In many instances their products play an analogous role to that of tetrapods, but some of them are specific for fish (Bentley, 1971). The hormonal regulation of water and ion homeostasis requires the participation and interaction of many endocrine systems at many levels. The following paragraph addresses a potential role of melatonin in this complicated picture.

Cortisol, prolactin and growth hormone have been well documented to be involved in osmoregulation in fish (Bentley, 1971). Diurnal and seasonal rhythms and the role of photoperiod in regulation of the hormone plasma levels were reported (Yada et al., 1991; Holloway et al., 1994; Björnsson et al., 1995; Pavlidis et al., 1999). Melatonin is known to be implicated in the control of rhythmic adaptations and affect endocrine gland function. Pinealectomy during the spring caused a reduction in plasma cortisol level of goldfish that was not observed in sham-operated fish. Moreover, during the summer pinealectomy resulted in higher plasma cortisol level in fish held under long photoperiod, but it had no effect in fish held under short photoperiod (Delahunty et al., 1977).

Recent studies show that alongside a classical circulating renin-angiotensin system (RAS), an intrarenal RAS operates in rainbow trout (Brown et al., 2000). Thus, melatonin may affect the circulating and/or intrarenal renin-angiotensin system in fish, in a way similar to that found in mammals. The potential interrelation between melatonin and AVT, a well-known osmoregulatory fish hormone, has been proposed (Kulczykowska, 1995, 1998, 1999; Kulczykowska et al., 2001). All these hormonal interactions may contribute to regulatory mechanisms of body fluid homeostasis in fish.

Conclusions and perspectives

To date, studies of the action of melatonin in fish have focused on its well-defined role in the time-keeping system. This paper suggests a new insight into melatonin's physiological function. The potential actions of melatonin at the level of major organs responsible for osmoregulation in fish: gill, gastrointestinal tract and kidney have been discussed. Moreover, the influence of melatonin on water/ion balance by affecting the circulatory blood hemodynamic and by interrelations with other hormones systems engaged in water/ion homeostasis has been considered. My studies on 2-[125 I]iodomelatonin binding in the kidneys and gills of freshwater rainbow trout and seawater flounder suggest the possibility of an action of melatonin at this sites. Potential targets for melatonin action in process of osmoregulation in fish are summarised in Figure 3.

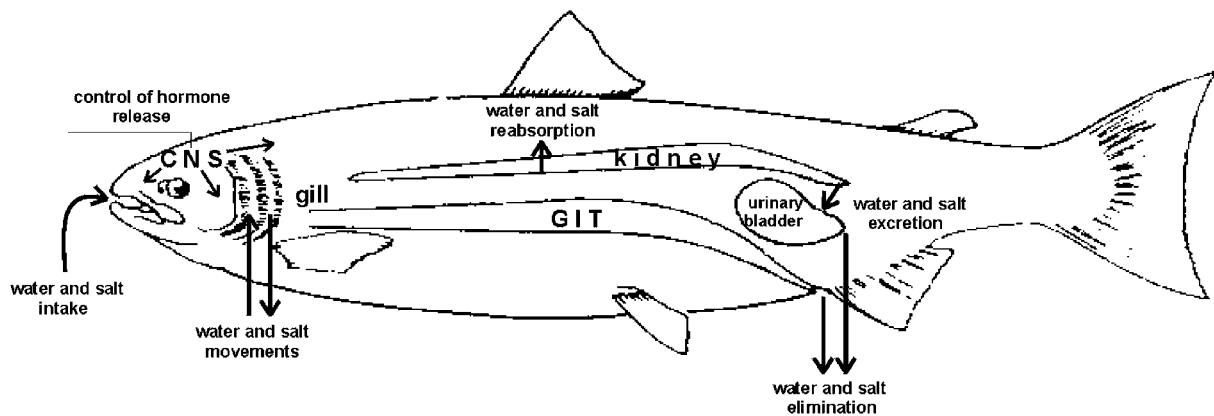


Figure 3. Potential targets for melatonin actions in process of osmoregulation in fish.

Whether melatonin directly and/or indirectly plays a role in regulation of water and ions balance in fish is still an open question. Further studies, not only in fish, but also in higher vertebrate classes, are essential to elucidate the mode of involvement of melatonin in osmoregulation processes. This would have important implications in understanding the regulation of body fluid homeostasis in vertebrates.

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