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Review

Melatonin: A potent candidate in the regulation of fish oocyte growth and maturation ☆

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ABSTRACT

Recent studies on several fish species, especially carp, implicated pineal hormone melatonin (*N*-acetyl-5-methoxytryptamine) as a potent candidate in the regulatory mechanism of seasonal reproduction. Under natural conditions, the temporal pattern of serum melatonin varied with daily light–dark cycle and the reproductive status of the fish as well. Carefully controlled study revealed that exogenous administration of melatonin may result in stimulation or inhibition or no influences at all on the gonadal functions depending on the reproductive status of fish. Cross-talk between the melatonin and ovarian steroid has been evident from *in vitro* study, in which melatonin accelerated the action of 17α,20β-dihydroxy-4-pregnen-3-one or maturation inducing hormone (MIH) on meiotic cell cycle resumption in carp oocytes by formation of maturation promoting factor (MPF) – a complex of two proteins, cyclin B and cyclin dependant kinase Cdk1. While several lines of evidence suggest melatonin effects on hypothalamo-hypophyseal–gonadal axis, localization and dynamics of a 37-kDa melatonin receptor protein in carp oocytes argued in favor of extra-hypothalamic direct action of melatonin on fish reproduction. A recent study in carp indicated that influences of an identical regimen of photoperiods in different parts of annual cycle on ovarian functions vary in relation to the profiles of serum melatonin, but not to any rhythm parameters of MT1 or MT2 receptors on the gonad or brain. The purpose of this short review is to bring together the current knowledge on the biological effects of melatonin on fish reproduction mainly focusing the recent findings on carp.

1. Introduction

Reproduction in most fish, like many other vertebrates, is discontinuous. Seasonally breeding fish species exhibit peak reproductive activity or spawning for a short period, which is preceded by a long and complicated process of preparation. The seasonal events in an annual reproductive cycle are often synchronized with periodic changes in one or more environmental components in such a way that breeding occurs in the most favorable part of the year [23]. Temporal organization of seasonal breeding is a species specific phenomenon, which may be a self-sustained circannual rhythmic function [5], or influenced by the environment [6]. Annual changes in the duration of the solar day or photoperiod has been proved to be the primary and regular variable that individually, or in combination with water temperature or other component(s) of environment, impel the 'driving function' in determining the sexual periodicity in most fish species that breed at mid- and high latitudes [1,6,22,48,69], and even at low latitudes [2,3,18,19].

The synchronization of reproductive events with the environment is mediated through a system, which is composed of sensors and circadian oscillators like the pineal organ, the lateral eyes and the suprachiasmatic nuclei (SCN) of the hypothalamus [50]. This circadian oscillator system among the fish species is located in the pineal organ and the eyes [24,27], among which the pineal organ for its ability of cyclic synthesis and release of melatonin (*N*-acetyl-5-methoxytryptamine) is considered as the most important component of its responsive mechanism to the changes in environmental light and darkness [22]. The daily pattern of melatonin secretion is conserved among vertebrates, as it is low during the daytime and high during the night, and thereby serves as the internal neuro-hormonal signal of darkness [50]. A recent study revealed that dark-induced melatonin synthesis in the carp pineal is a multi-neuronal function, in which both adrenergic (α1 and β1, but not α2) and dopaminergic signals are stimulatory, whereas cholinergic signals are inhibitory [55]. Melatonin is recognized as the biological timekeeping hormone mainly due to the fact that it reflects the seasonal variations in day-length across the whole animal kingdom, rather than the existence of direct evidences of its role in the entrainment of reproduction in fishes [39]. However,

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over the past few decades, the role of melatonin in the regulation of fish reproduction remained far from being clear mainly due to insufficient data collected from well designed carefully controlled studies in the same species. Few recent studies provided evidence that melatonin interacts with the reproductive cascade at a number of key steps such as through the central hypothalamo-hypophyseal system as well as modulates actions of sex steroids in the final oocyte maturation. Moreover, reports on receptor independent free-radical scavenging actions of melatonin added further interest in the physiology and pathophysiology of gonadal functions in vertebrates [58]. This short review thus aims to bring together the current knowledge on the role of melatonin in the regulation of fish reproduction mainly focusing on temporal relationship between the circulating profiles of melatonin and its receptors on target tissues, gonadal responsiveness to exogenous melatonin, interplay between melatonin and other hormones during oocyte maturation, dynamics of melatonin receptors and role of several recently discovered novel hypothalamic peptides as well, and shape the current working hypotheses supported by recent findings on teleosts.

2. Implication of daily circulating profiles of melatonin in seasonal reproduction

Circadian profiles of melatonin in the blood are determined by the prevailing light–dark cycle [21,39]. As a consequence, circulating melatonin levels are higher at night than during the day irrespective of the habit and habitat of the species so far examined [51]. This pattern of melatonin rhythms is conserved across all vertebrates. However, three variants of nocturnal melatonin profiles, namely type-A, -B and -C profiles have been identified in different vertebrates, including fish [22,39]. The A-type profiles are characterized by a discrete peak in late dark phase e.g., Atlantic cod *Gadus morhua* [48], haddock *Melanogrammus aeglefinus* [14], whereas B-type profiles are characterized by a discrete peak in the mid dark phase e.g., Nile tilapia *Oreochromis niloticus niloticus* [36], and the C-type is characterized by a rapid rise in melatonin immediately following the onset of the dark period e.g., Atlantic salmon *Salmo salar*, rainbow trout *Onchorhynchus mykiss*, Atlantic halibut *Hippoglossus hippoglossus* and most teleosts [22,39]. Though the etiology of these different types of melatonin profile is far from being clearly understood, it might be linked to the ability or not to anticipate photic signals under the control of circadian clocks [36]. Indeed, many studies highlighted the environmental regulation of daily and annual melatonin variations such as light, temperature and salinity as well as self-sustained endogenous rhythms [33,39]. However, the study on carp revealed for the first time that the nocturnal peak pattern of serum melatonin in the same species may vary from A-type (during the preparatory phase) to B-type (in the remaining part of the annual cycle) in relation to reproductive phase (Fig. 1) in an annual cycle [12,13,35]. Obviously, the study offers an indirect evidence of a functional relationship between the profiles of endogenous melatonin and the gonadal functions in carp. Such hypothesis earned support from a study on carp held under natural conditions demonstrating a significant negative correlation between the seasonal peak values of serum melatonin and two major ovarian steroids, i.e., 17-β estradiol (E_2) and 17α,20β-dihydroxy-4-pregnen-3-one (17α,20β DHP) or maturation inducing hormone (MIH) [12] and provided basis of further experimental study. Various lines of evidence are now available to suggest a cross-talk between the melatonin and ovarian steroid in the regulation of fish oocyte maturation. However, any study on influences of reproductive hormones on melatonin synthesis in the fish pineal is not yet known and thus remains as an interesting topic for future research.

3. Influences of melatonin in the regulation of seasonal reproductive events

Growth and development of gonads in fish comprise of sequential events in an annual cycle. Primarily, on the basis of gametogenic status of gonads, the annual breeding cycle in fish is divided into four different phases, like (a) the preparatory phase, (b) the pre-spawning phase, (c) the spawning phase, and (d) the post-spawning phase. Each phase has a specific duration and is characterized by distinct germ cell profiles in the ovary [18] and the testis [3]. The ovaries exhibit mostly oogonia and few stage-I primary oocytes during the preparatory phase; stage-II oocytes as the most advanced germ cells in the pre-spawning phase; yolk-laden stage-III oocytes in the spawning phase; and a large number of atretic or post-ovulatory follicles in the post-spawning phase (Fig. 2). In males, during the preparatory phase recrudescence of gametogenesis occurs with stage-I spermatids as the most advanced germ cell, while advancement of germ cell development beyond spermatid-I stage occurs during the pre-spawning phase. The peak in gametogenetic activity is attained during the spawning phase, followed by a sudden fall in testicular activities in the post-spawning phase. Obviously, several studies addressed the question whether pineal or its hormone melatonin plays a critical role in determining the transition of one reproductive phase to the other, but led to conflicting conclusions [6,21] largely because of diverse experimental designs followed in different fish species or, lack of sufficient information on physiological status of the same species. However, subsequent studies provided convincing data to suggest a significant role of melatonin in the regulation of fish reproduction.

Surgical removal of the pineal or pinealectomy is one of the most primitive techniques followed to understand the importance of this organ and its hormone melatonin in the control of reproduction. But the results have been diverse. Pinealectomy accelerated sexual maturation in *Ictalurus punctatus* [15], *Heteropneustes fossilis* [28], *Channa punctatus* [29], but no such effects of pinealectomy were found in *Gasterosteus aculeatus*, *Astyanax mexicanus*, *Fundulus heteroclitus*, and *Carassius auratus* [31]. Reproductive phase dependent effects of pinealectomy were noted in *Clarias batrachus* [32], *H. fossilis* [28] and *C. punctatus* [29]. Popek et al. [46] demonstrated that removal of pineal during vitellogenesis distorts the steroidogenic function of ovaries resulting in diminished estradiol secretion. Melatonin is suggested to play an important role in the regulation of vitellogenesis, during which the yolk precursor protein (vitellogenin) is synthesized in the liver under the influence of estrogens followed by its active incorporation into the developing oocytes [68]. However, pinealectomy and melatonin treatment in rainbow trout failed to induce gene expressions of estrogen receptors and vitellogenin [38].

The effects of pinealectomy also varied in relation to the photothermal conditions to which the fish were held. In most fish species, pinealectomy stimulated gonadal development when exposed to short photoperiods, but inhibited when exposed to long photoperiods. In catfish [25], the effects of pinealectomy varied with photoperiods and the reproductive phase, as ovarian recrudescence was accelerated under long photoperiods (LD 14:10 at 25 °C), but unaltered under short photoperiods (LD 9:15 at 25 °C) during the preparatory period and no effects were found during the pre-spawning and spawning periods. On the contrary, no role of the pineal in the regulation of reproduction was found in *F. heteroclitus*, as they were capable of perceiving stimulatory or inhibitory photoperiods regardless of the presence or absence of the pineal [16]. Exposure of pinealectomized catfish to continuous light (LL) or constant darkness (DD) did not result in any changes in the testosterone level [32].