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Steroids in teleost fishes: A functional point of view

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ABSTRACT

Steroid hormones are involved in the regulation of a variety of processes like embryonic development, sex differentiation, metabolism, immune responses, circadian rhythms, stress response, and reproduction in vertebrates. Teleost fishes and humans show a remarkable conservation in many developmental and physiological aspects, including the endocrine system in general and the steroid hormone related processes in particular. This review provides an overview of the current knowledge about steroid hormone biosynthesis and the steroid hormone receptors in teleost fishes and compares the findings to the human system. The impact of the duplicated genome in teleost fishes on steroid hormone biosynthesis and perception is addressed. Additionally, important processes in fish physiology regulated by steroid hormones, which are most dissimilar to humans, are described. We also give a short overview on the influence of anthropogenic endocrine disrupting compounds on steroid hormone signaling and the resulting adverse physiological effects for teleost fishes. By this approach, we show that the steroidogenesis, hormone receptors, and function of the steroid hormones are reasonably well understood when summarizing the available data of all teleost species analyzed to date. However, on the level of a single species or a certain fish-specific aspect of physiology, further research is needed.

1. Introduction

Bony fishes (osteichthyes) are a very successful class of vertebrates with over 25,000 living species [1]. The first osteichthyes emerged about 450 million years ago and since then, a tremendous diversity of species has evolved [2]. Osteichthyes are subdivided into lobe-finned fishes (sarcopterygii) and ray-finned fishes (actinopterygii) [2]; among the latter the teleostei are the most representative [3] and best studied group [1]. Teleost fishes have adapted to diverse ecological habitats ranging from fresh water over seawater to environmental extremes (e.g., emerging onto land) [1].

Teleost fishes are of high interest for humans in two large areas, namely as part of the diet and as model organisms for research purposes. For humans, fishes have been and are still an important nutritional resource: on the one hand, the evolution of hominids and the early brain development was dependent on fish-rich food, and on the other hand, humans are still reliant on essential nutrients provided in high concentrations in fishes [4,5]. However, due to overfishing and other environmental factors like pollution or ocean acidification, wild stocks of fishes were dramatically decreased [4,6]. To respond to declining wild populations and increased demand for seafood, aquaculture has grown and is still growing [4,7]. The number of species cultured for human nutrition, however, is relatively small [1,7].

The second aspect, where fishes in general and teleost fishes in particular are of importance for humans, is their usage in research as model organisms. The basal processes underlying embryogenesis and organogenesis are strikingly conserved between teleost fishes and tetrapods [8–11]. The understanding of vertebrate development has advanced considerably by studying model organisms, among these are also teleost fishes [12,13]. The most popular fish model species are also increasingly used to analyze human diseases like genetic disorders [14], brain disorders [15,16], or toxicological [17] and immunological [18] aspects, among others [9,19]. Teleost fishes share not only developmental aspects with their mammalian counterparts, but also the endocrine system including hormones, receptors, and signaling cascades displays a striking homology [9,20]. Compared to mammalian model organisms like mouse and rat, the widely used teleost fish species like zebrafish,

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medaka, fathead minnow, or three-spined stickleback have several practical advantages [10,12,21]. Their small size allows for large fish stocks in relatively small facilities. The fishes have a high fecundity, fertilize externally, their embryos are often optically transparent thus enabling microscopic observations, the embryonic development occurs rapidly, and both adults as well as embryos are amenable to genetic modifications like microinjection, chemical mutagenesis, and transgenesis [10,19,22–25]. Furthermore, most endocrine hormones and receptors are prenatally active in mammals, which impair the investigation of their developmental role in mammals. Here, teleost fishes represent an ideal model for the analysis of prenatal hormone action [20].

However, when working with teleost fishes, one has to consider that the lineage of teleostei underwent whole genome duplication about 350 million years ago, a process that did not occur in terrestrial vertebrates and is as such termed the teleost specific whole genome duplication [26–28]. This offers a unique opportunity to study evolutionary processes in teleost fishes [20]. It is considered that genome duplications are crucial for the generation of complexity and for the provision of raw material for adaptation and innovation [28]. After a whole genome duplication event, the duplicated gene copies can have different fates. Non-functionalization by silencing mutations is the most likely outcome, but it is also common that the duplicated genes are preserved by subfunctionalization (i.e., division of gene function on both copies), neofunctionalization (i.e., gaining a novel function), and parallel existence with diverging regulation and expression [28–30]. All of these processes have been observed in teleost fishes [28].

Due to the marked conservation in many developmental and physiological aspects between fishes and mammals, fishes were long considered as simply being "aquatic mammals", which is not true [31]. For instance, teleost fishes have developed a large variety of reproductive strategies for adaptation to differing aquatic environments [32] and show an enormous plasticity concerning sexual determination processes [33,34], which is in contrast to mammals. Therefore, especially the endocrinology of teleost fishes compared to mammals in general and humans in particular has to be different in certain aspects. In this review, we will focus on the endocrinology and specifically on the steroid hormones of teleost fishes (the list of covered species and their taxonomy can be found in Appendix A, Supplementary data, Table S1). We will give an overview of steroidogenesis and steroid hormone receptors in teleost fishes and compare the obtained knowledge to the human system. Further, we will review the implications of the duplicated genome on the steroid biosynthesis and the steroid hormone receptors. The steroid hormone related processes, which are most dissimilar to the human system, will be illustrated as well as the effects occurring upon disruption of endocrine signaling. This review will highlight conserved and dissimilar aspects of steroid hormones in teleost fishes compared to humans and will point out that the research on these model organisms is beneficial for the well-being of the human population.

2. Synthesis of steroid hormones in teleost fishes compared to human steroidogenesis

In general, steroid biosynthesis in teleost fishes is controlled by the hypothalamus–pituitary–interrenal and the hypothalamus–pituitary–gonadal axis [9,35,36]. Steroidogenesis occurs primarily in different peripheral tissues like the gonads, the interrenal gland, and the brain [37–41]. The interrenal gland comprises specialized cells which are embedded in the head kidney of teleost fishes and is functionally homologous to the adrenal gland in mammals [42]. All classes of steroid hormones are synthesized *de novo* from the common precursor cholesterol [43,44]. Its availability for the cytochrome p450 side chain cleavage enzyme (Cyp11a1), which removes the side chain of cholesterol resulting in pregnenolone, is controlled by the steroidogenic acute regulatory protein (StAR) [45,46]. StAR transfers cholesterol across the barrier of the outer and inner mitochondrial membrane and is as such the rate limiting step of steroidogenesis [47]. Downstream of the synthesis pathway, several enzymes modify the steroid nucleus including side chain cleavage, Δ5/Δ4-isomerization, hydrogenation, and aromatization. Other enzymes add and modify functional groups by hydroxylation, reduction, or oxidation [48]. The postulated pathway of steroidogenesis in teleost fishes is outlined in Fig. 1. To date, all of the denoted genes are identified in a large number of different teleost species (see Table 1) and annotated in even more species. Most of those genes are cloned and their expression has been analyzed; however, the extent of characterization is strongly dependent on the gene, on the species, and on the focus of the respective study (Table 1 and references therein). For example, the cytochrome p450 enzymes cholesterol side chain cleavage (*cyp11a1*), 17α-hydroxylase/lyase (*cyp17a*), and aromatase (*cyp19a1*) are the best characterized genes in the pathway, because they constitute three important bottlenecks in the steroidogenesis. Cyp11a1 is the only enzyme that converts cholesterol to pregnenolone and is therefore the only entrance into the whole process of steroidogenesis. Cyp17a is the next bottleneck in the pathway, because it is the only enzyme responsible for the conversion of C21 steroids to C19 steroids. This enzyme can use a variety of substrates, but the two most important products (17α-hydroxyprogesterone and androstenedione) cannot be synthesized by other enzymes. Cyp19a1 is responsible for the formation of C18 steroids and is thus the most important enzyme in regard of hormonal control of sexual development in teleost fishes [49–51]. In contrast to the aforementioned important genes which have been deeply characterized or have been at least annotated in almost all teleost fish species analyzed to date, there are other genes in the pathway, which are only characterized in a few selected species. Among these genes are 17β-hydroxysteroid dehydrogenases type 3 and type 1 (*hsd17b3* and *hsd17b1*, respectively), and 21-hydroxylase (*cyp21a1*). Hsd17b3 is an essential enzyme for the synthesis of 11-ketotestosterone, the active androgen in fish [52], and has been characterized only in zebrafish and medaka up to now [52–54]. Due to sequence homology, the gene has been annotated in a number of further teleost species (Table 1). Hsd17b1 converts inactive estrone (E1) to active, receptor-binding estradiol (E2), and was identified and partially characterized in a few model fish species like Nile tilapia [55], Japanese eel [56], zebrafish [53,57], and Atlantic cod [58]. Similar to *hsd17b3*, *hsd17b1* is also annotated based on sequence similarity in many further teleost fish species (Table 1). The steroid 21-hydroxylase (*cyp21a1*) is by far the least characterized gene in the steroidogenic pathway of teleost fishes. This enzyme is supposed to be involved in the biosynthesis of 11-deoxycorticosterone and cortisol, where the latter is a deeply investigated stress hormone in teleost fishes [59]. Therefore, it is surprising that the mRNA was only detected in five fish species and that no functional evidence for this enzyme is shown and published to date (Table 1).

While all the genes associated with steroidogenesis in teleost fishes are known and the respective mRNAs were detected in various species (Table 1), the verification of the postulated pathway with respect to the function, i.e., the enzymatic level, is lagging behind. When summarizing the published evidence for all enzymes of the steroidogenic pathway over all teleost species, about 70% of the postulated reactions have been directly proven (Fig. 1, Table 1). However, when a single species is considered, the maximum coverage is only approximately 20–40% of the steroidogenic pathway, depending on the species. The maximum individual coverage is observed in well characterized model

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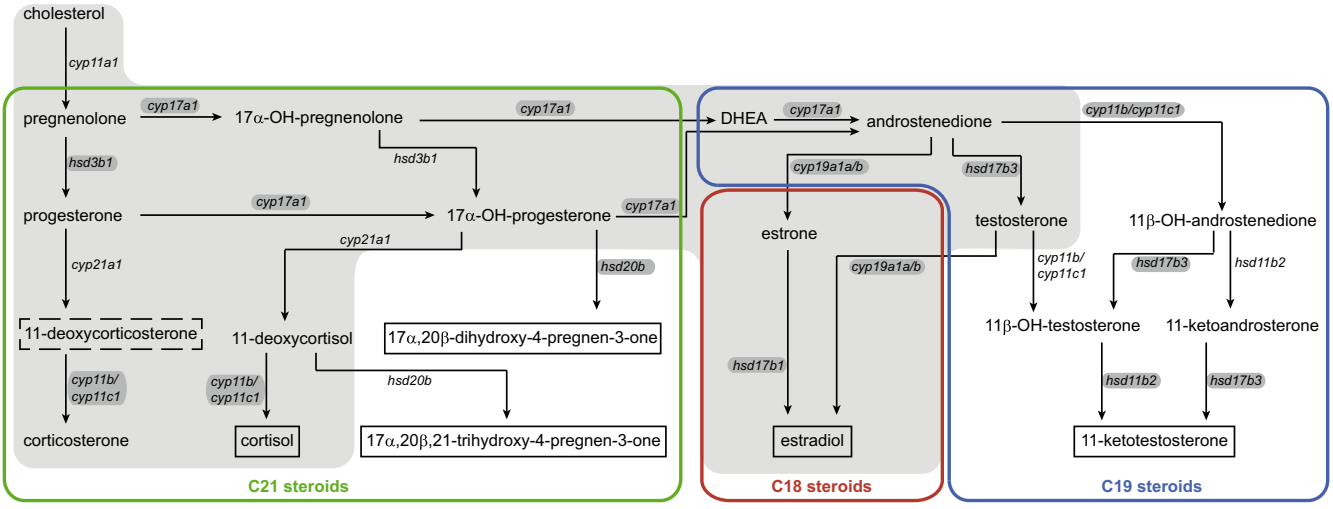

Fig. 1. Postulated pathway of steroidogenesis in teleost fishes. Steroids are grouped according to the number of carbon atoms in the steroid nucleus. The core pathway of steroidogenesis, which is similar to humans, is highlighted in light gray. Gene names of supposed enzymes are denoted on each arrow. *Cyp11b* is the respective gene for most teleost fishes, while *cyp11c1* is the ortholog only for zebrafish. Those steroids, which are putative physiological ligands for receptors, are framed, and the putative ligand for the mineralocorticoid receptor is framed dashed. Enzymes that have been experimentally demonstrated to catalyze the denoted reaction are highlighted in gray. For source data and details on the enzymatic activity, the reader is referred to Table 1. Abbreviations are: cyp, cytochrome P450; DHEA, dehydroepiandrosterone; hsd, hydroxysteroid dehydrogenase; OH-, hydroxy-.

organisms like Nile tilapia, Japanese eel, rainbow trout, and medaka. Strikingly, in the zebrafish, which is increasingly used as model organism for human endocrinology and for endocrine disruption studies [9,19,23], only a small part of the steroidogenic pathway has been shown to be enzymatically functional [48]. Comparable to the observations mentioned above on the detection of mRNA, certain enzymes are better characterized on the functional level than others. Those reactions catalyzed by Cyp19a1 and Cyp17a are the best characterized and were also analyzed in a broad variety of fish species (Table 1). Interestingly, the carbonyl reductase-like 20β-hydroxysteroid dehydrogenase (Hsd20b) ranges among the best functionally characterized enzymes, although only one of putatively two catalyzed reactions was investigated to date. For two enzymes of the whole pathway, the analysis for enzymatic activity is still lacking. Cyp21a1 is supposed to catalyze the conversion of progesterone and 17α-hydroxyprogesterone to 11-deoxycorticosterone and 11-deoxycortisol, respectively, but proof for these reactions is missing completely. The side chain cleavage enzyme Cyp11a1 is supposed to generate pregnenolone from cholesterol; however, experimental evidence for this reaction is lacking until now. Only the conversion of 25-hydroxycholesterol to pregnenolone *in vitro* by the Cyp11a1 enzymes from rainbow trout [60] and Japanese eel [61] could be shown. However, based on the knowledge for the human CYP11A1 [62], the *in vivo* substrate of Cyp11a1 from teleost fishes is probably cholesterol itself and not the 25-hydroxylated form.

When the pathway for steroid biosynthesis of teleost fishes is compared to the steroidogenesis in *Homo* sapiens [44], a remarkable conservation in the core part of the pathway is noticed (Fig. 1), but also differences in three major areas. These are firstly the aldosterone biosynthesis in humans, secondly the synthesis of maturation inducing steroids in teleost fishes, and thirdly the diverging pathways of androgen biosynthesis. In teleost fishes, corticosterone is an endpoint of a synthesis pathway as shown in Fig. 1. In contrast, in humans corticosterone is rather an intermediate steroid for the biosynthesis of aldosterone. Aldosterone induces the resorption of sodium and chloride ions, stimulates the retention of water, and activates the secretion of potassium, hydrogen, and ammonium ions by acting through the mineralocorticoid receptor (MR) [63]. The MR has been identified in teleost fishes and can be activated by 11-deoxycorticosterone and cortisol [64–66]. However, teleost fishes seem to lack aldosterone, because the hormone itself was not detected so far in these fishes [67,68] and an enzyme synthesizing aldosterone has not been identified [21,68–71]. Consequently, the identity of a potential MR ligand as well as the necessity for a MR ligand in teleost fishes is controversially discussed [9,68,72,73].

A part of the steroidogenesis pathway which is unique to teleost fishes is the biosynthesis of the maturation inducing steroids (MIS) 17α,20β-dihydroxy-4-pregnen-3-one (17,20β-P, or DHP) and 17α,20β,21-trihydroxy-4-pregnen-3-one (20β-S) by Hsd20b from 17α-hydroxyprogesterone and 11-deoxycortisol, respectively. 17,20β-P is acting as MIS mostly in salmoniformes, cypriniformes, siluriformes, and atheriniformes, while 20β-S is the MIS in many perciformes [74,75]. These steroids induce the oocyte maturation in teleost fishes and do not exist in humans. Also, the gene responsible for MIS synthesis, *hsd20b*, has so far been only identified in teleost fishes, but not in humans.

The largest differences between the steroidogenesis of teleost fishes and humans can be found in the area of the androgens. The ligand for the androgen receptor (AR) in teleost fishes is 11-ketotestosterone (11-KT) [31,76–79], while in humans testosterone (T) and the even more potent hormone 5α-dihydrotestosterone (DHT) are the active androgens [80–82]. Thus, this difference results in distinct biosynthesis pathways. In teleost fishes, 11-KT is synthesized via 11β-hydroxy-androgens (Fig. 1). These metabolites do not occur in humans, because the human androgenic pathway is focused on 5α- and 3α- reductions [44]. Further, the expression pattern and substrate preferences of conserved enzymes differ between fishes and humans. For instance, human 17β-hydroxysteroid dehydrogenase type 3 is almost exclusively expressed in testis [83], while the zebrafish ortholog demonstrates a more widespread expression pattern [52]. Both enzymes were shown *in vitro* to catalyze the conversion of androstenedione to testosterone and 11-ketoandrosterone to 11-ketotestosterone, although the latter reaction does not occur *in vivo* in humans. In contrast, the zebrafish Hsd17b3 was not able to convert androsterone to androstanediol, a reaction readily catalyzed by human HSD17B3 [52]. The most obvious difference between teleost fishes and humans in the area of androgens, being the usage of 11-KT

Table 1
Evidence for mRNA expression and enzymatic activity for steroidogenic genes in teleost fish species.

Gene	mRNA detected		Enzymatic activity evidenced		Gene only annotated in species*
	Species	References	Reaction catalyzed	Reference	
cyp11a1/2	*Oryzias latipes*	[54,208,265,266]			
	Oncorhynchus kisutch	[267]			
	Danio rerio	[39,53,89,106,268–271]			
	Gadus morhua	[58,109,272]			
	Acanthopagrus schlegeli	[273]			
	Epinephelus coioides	[274]			
	Gobiocypris rarus	[275]			
	Ictalurus punctatus	[276]			
	Sparus aurata	[277]			
	Oncorhynchus mykiss	[60,278]	25-Hydroxycholesterol → pregnenolone	[60]	
	Anguilla japonica	[61,279]	25-Hydroxycholesterol → pregnenolone	[61]	
	Amphiprion clarkii	[280]			
	Salmo salar	[281]			
	Oncorhynchus tshawytscha	[282]			
hsd3b1	*Cyprinus carpio*	[47]			*Stegastes partitus*, *Cynoglossus semilaevis*, *Larimichthys crocea*
	Oryzias latipes	[54,208,266]			
	Oncorhynchus kisutch	[267]			
	Anguilla japonica	[61,283]	Pregnenolone → progesterone	[283]	
	Oreochromis niloticus	[284]	Pregnenolone → progesterone	[284]	
	Danio rerio	[39,53,106,268,269]			
	Acanthopagrus schlegeli	[273]			
	Epinephelus coioides	[274]			
	Gobiocypris rarus	[275]			
	Ictalurus punctatus	[276]			
	Oreochromis mossambicus	[285]			
	Oncorhynchus mykiss	[286]	Pregnenolone → progesterone	[286]	
	Sparus aurata	[277]			
	Oncorhynchus tshawytscha	[282]			
	Gadus morhua	[109]			
cyp21a1	*Cyprinus carpio*	[47]			
	Oryzias latipes	[208]			
	Danio rerio	[89]			
	Sciaenops ocellatus	[287]			
	Oreochromis mossambicus	[285]			
cyp17a1/2	*Cyprinus carpio*	[47]	17α-Hydroxyprogesterone → androstenedione	[288]	*Takifugu rubripes*, *Gasterosteus aculeatus*
	Oryzias latipes	[54,98,208,289]	Pregnenolone → 17α-hydroxypregnenolone → DHEA; progesterone → 17α-hydroxyprogesterone → androstenedione	[98]	
	Pimephales promelas	[110]			
	Oncorhynchus kisutch	[267]			
	Oreochromis niloticus	[97]	17α-Hydroxyprogesterone → androstenedione; 17α-hydroxypregnenolone → DHEA	[97]	
	Danio rerio	[39,53,89,290,291]			
	Dicentrarchus labrax		17α-Hydroxyprogesterone → androstenedione	[292]	
	Oncorhynchus mykiss	[293]	Pregnenolone → 17α-hydroxypregnenolone → DHEA; progesterone → 17α-hydroxyprogesterone → androstenedione	[293]	
	Cynoglossus semilaevis	[294]			
	Acanthopagrus schlegeli	[273]			
	Clarias gariepinus	[295]	Progesterone → 17α-	[295]	

Table 1 (*continued*)

Gene	mRNA detected		Enzymatic activity evidenced		Gene only annotated in species*
	Species	References	Reaction catalyzed	Reference	
			hydroxyprogesterone → androstenedione		
	Verasper moseri	[96]			
	Paralichthys olivaceus	[296,297]			
	Sebastes schlegeli	[298]			
	Epinephelus coioides	[274]			
	Gobiocypris rarus	[275]			
	Anguilla japonica	[61,99]	Pregnenolone → 17α-hydroxypregnenolone → DHEA; progesterone → 17α-hydroxyprogesterone → androstenedione	[99]	
	Ictalurus punctatus	[276]			
	Pimephales promelas	[299]			
	Monopterus albus	[300]			
	Oreochromis mossambicus	[285]			
hsd20b	*Oncorhynchus mykiss*	[301,302]	17α-Hydroxyprogesterone → 17α,20β-dihydroxy-4-pregnen-3-one	[301,303]	
	Oreochromis niloticus	[304]	17α-Hydroxyprogesterone → 17α,20β-dihydroxy-4-pregnen-3-one	[304]	
	Clarias gariepinus	[305]			
	Danio rerio	[306]			
	Cyprinus carpio		17α-Hydroxyprogesterone → 17α,20β-dihydroxy-4-pregnen-3-one	[288]	
	Anguilla japonica		17α-Hydroxyprogesterone → 17α,20β-dihydroxy-4-pregnen-3-one	[307]	
	Acanthopagrus latus	[308]			
	Gadus morhua	[272]			
cyp11b/cyp11c1	*Danio rerio*	[309–312]			*Poecilia reticulata*
	Oryzias latipes	[208,289]			
	Anguilla japonica	[69]	11-Deoxycortisol → cortisol; 11-deoxycorticosterone → corticosterone	[69]	
	Oreochromis niloticus	[163,313]			
	Oncorhynchus mykiss	[129,314]			
	Sciaenops ocellatus	[287]			
	Dicentrarchus labrax	[292,315,316]	Androstenedione → 11β-hydroxyandrostenedione	[292]	
	Cyprinus carpio		Androstenedione → 11β-hydroxyandrostenedione	[288]	
	Sparus aurata	[277]			
	Oncorhynchus tshawytscha	[282]			
cyp19a1a/b	*Odontesthes bonariensis*	[170]			*Poecilia reticulata*, *Haplochromis burtoni*, *Neolamprologus brichardi*, *Astyanax mexicanus*, *Poecilia formosa*, *Stegastes partitus*, *Larimichthys crocea*, *Notothenia coriiceps*, *Esox lucius*, *Cynoglossus semilaevis*
	Oryzias latipes	[54,208,317]	Testosterone → estradiol	[317]	
	Pimephales promelas	[110,318,319]			
	Oncorhynchus kisutch	[267]			
	Carassius auratus	[320,321]	Androstenedione → estrone	[320]	
	Danio rerio	[39,53,89–91,311,312,322–325]			
	Onchorhynchus mykiss	[129]			
	Oreochromis niloticus	[313,326]	Testosterone → estradiol	[326]	
	Dicentrarchus labrax	[315,316]			
	Takifugu rubripes	[51]			
	Porichthys notatus	[160]			
	Salmo salar	[281,327]			
	Tautogolabrus adspersus		Androstenedione → estrone	[50]	
	Jenynsia multidentata	[328]			

(*continued on next page*)

Table 1 (*continued*)

Gene	mRNA detected		Enzymatic activity evidenced		Gene only annotated in species*
	Species	References	Reaction catalyzed	Reference	
	Heteropneustes fossilis		Testosterone → estradiol	[329]	
	Centropristis striata	[330]			
	Gadus morhua	[58,272]			
	Acanthopagrus schlegeli	[273]	Androstenedione → estrone	[273]	
	Epinephelus coioides	[274]			
	Gobiocypris rarus	[275]			
	Ictalurus punctatus	[276]			
	Oreochromis mossambicus	[285]			
	Sparus aurata	[277]			
	Haplochromis burtoni	[49]			
	Ctenochromis horei	[49]			
	Pseudotropheus pulpican	[49]			
	Haplochromis obliquidens	[49]			
	Ophthalmotilapia ventralis	[49]			
	Enantiopus melanogenys	[49]			
	Perissodus microlepis	[49]			
	Neolamprologus pulcher	[49]			
	Altolamprologus fasciatus	[49]			
hsd17b3	*Danio rerio*	[52,53,200]	Androstenedione → testosterone; 11β-hydroxyandrostenedione → 11β-hydroxytestosterone; 11-ketoandrosterone → 11-ketotestosterone	[52]	*Poecilia reticulata*, *Stegastes partitus*, *Poecilia formosa*, *Astyanax mexicanus*, *Esox lucius*, *Notothenia coriiceps*, *Larimichthys crocea*
	Oryzias latipes	[54]			
hsd17b1	*Oreochromis niloticus*	[55]	Estrone → estradiol	[55]	*Esox lucius*, *Notothenia coriiceps*, *Larimichthys crocea*, *Poecilia reticulata*, *Cynoglossus semilaevis*, *Stegastes partitus*, *Poecilia formosa*, *Oryzias latipes*
	Anguilla japonica	[56]	Estrone → estradiol	[56]	
	Danio rerio	[53,57]	Estrone → estradiol	[57]	
	Gadus morhua	[58]			
hsd11b2	*Cyprinus carpio*	[47]			*Esox lucius*, *Cynoglossus semilaevis*, *Stegastes partitus*, *Astyanax mexicanus*
	Odontesthes bonariensis	[120,170]			
	Pimephales promelas	[110,319]			
	Onchorhynchus mykiss	[331]	11β-Hydroxytestosterone → 11-ketotestosterone	[331]	
	Clarias gariepinus	[332]	11β-Hydroxytestosterone → 11-ketotestosterone	[332]	
	Danio rerio	[309,310,333,334]			
	Oryzias latipes	[289]			
	Gobiocypris rarus	[275]			
	Salmo salar	[335]			

The list of references in this table is not exhaustive.
Abbreviations: cyp, cytochrome P450; DHEA, dehydroepiandrosterone; hsd, hydroxysteroid dehydrogenase.
* The entries in this column were derived from a search in the GENE database of the NCBI in February 2015.

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instead of T and DHT, seems to become a little challenged, because recently DHT was detected in plasma of fathead minnow and found to have androgenic potency [84,85]. Since DHT was so far only detected in this single species, its physiological role for fathead minnow in particular and teleost fishes in general needs further investigation [86].

As already mentioned in the introduction, the lineage of ray-finned fishes underwent a whole genome duplication, which did not occur in terrestrial vertebrates [26,27]. Duplicated genes can have different fates like silencing by mutations thereby preventing expression, neofunctionalization by gaining a beneficial function, or a parallel existence with diverging regulation and expression [28–30]. Regarding the genes for steroidogenesis in teleost fishes, there is no general statement to be made for the fate of the duplicated copies. Zebrafish for instance seem to have lost or silenced many duplicated genes [20,48], while other species have retained many functional copies [1,87,88]. However, the subjection of duplicated genes to differential regulation and expression in a tissue- and developmental stage-dependent manner seems to be a common phenomenon regarding steroidogenic genes in teleost fishes, as discussed for a few exemplary genes in the following. In Nile tilapia, two genes for StAR have been identified, where StAR1 seems to be responsible for the steroidogenesis in the head kidney, while StAR2 is probably involved in the estrogen production during early sex differentiation in the gonads [40]. Besides, both genes might be required for androgen synthesis in adult testes [40]. The well-characterized aromatase gene (*cyp19a1*) is another example for the parallel existence of duplicated genes [87]. Cyp19a1a is the ovarian aromatase, while Cyp19a1b is the neuronal aromatase with strong expression in the brain [87,89,90]. Beside showing a tissue-specific expression pattern, both gene copies have also evolved different inducibility, because the expression of brain aromatase can be stimulated by estradiol, while the expression of the ovarian aromatase not [89,91–94]. Although both gene copies are differentially expressed and regulated, the catalyzed reaction of both aromatases is identical [95]. This is in contrast to the duplicated *cyp17a* gene from some teleost fishes [96]. In humans, CYP17A1 acts as 17α-hydroxylase and 17,20-lyase and the distinction between these reactions is functional and not genetic [44]. Medaka and Nile tilapia Cyp17a1 were shown to possess both 17α-hydroxylase and 17,20-lyase activity, similar to the human enzyme, since they catalyzed the conversion of pregnenolone to DHEA via 17α-hydroxypregnenolone and the conversion of progesterone to androstenedione via 17α-hydroxyprogesterone [97,98]. However, the Cyp17a2 from both species were only able to convert pregnenolone and progesterone to the respective 17α-hydroxylated products, but were unable to produce DHEA or androstenedione, thus lacking the 17,20-lyase activity [97,98]. Whether this observation holds true for all teleost fish species, needs further elucidation. In Japanese eel, for instance, only one Cyp17a was identified to date, which possesses both 17α-hydroxylase and 17,20-lyase activity [99]. It is possible that the duplicated gene has been silenced during the eel evolution, or simply awaits its identification.

3. Receptors for steroid hormones in teleost fishes

In vertebrates, steroid hormones exert their actions in a genomic or a non-genomic manner. The classical genomic action involves the binding of the steroid hormones to the respective cytosolic nuclear receptors, which translocate to the nucleus and bind to their respective response elements on the genomic DNA thereby regulating transcription [100,101]. The non-genomic action of steroid hormones, which occurs much faster [102], is mediated by membrane bound receptors on the cell surface and initiates rapid intracellular responses [103,104]. Similar to humans, teleost fishes possess a full complement of nuclear receptors (Table 2) as well as non-classical membrane bound steroid receptors [103]. The classical nuclear receptors are surprisingly well characterized regarding their expression patterns and ligand binding properties in a large variety of teleost species (Table 2). Similar to the observations concerning steroid biosynthesis genes described above, in many teleost fishes duplicated genes for nuclear receptors were identified, while in other fish species up to now only one gene was described. Further, for some nuclear receptor genes splice variants have been demonstrated, which is comparable to the human situation but adds another layer of complexity to the nomenclature systems as well as to the physiological roles. This can be illustrated on the glucocorticoid receptor (GR): in the common carp [105], Nile tilapia [106], and rainbow trout [107] two GR genes were found (GR1 and GR2), while in zebrafish [108], Atlantic cod [109], and fathead minnow [110] only one GR gene was characterized. In zebrafish, the existence of splice variants of the GR gene (GRα and GRβ) have been reported [108], where the GRβ acts as a dominant negative inhibitor on the transactivational activity of the canonical GRα [111]. The currently characterized GR subtypes from teleost fishes have been shown to bind cortisol with high affinity (see references in Table 2). Strikingly, the rainbow trout GR [112] and the GR from Burton's mouthbrooder [113] were found to bind cortisone and aldosterone, respectively; however, with a remarkable lower affinity than cortisol.

The MR in teleost fishes is derived from a single gene. Only in rainbow trout, two forms (MRa and MRb) have been cloned and characterized [65]; however, due to their high sequence similarity, it is most likely that both forms are splice variants from a single gene. Similar to the human MR, which can bind cortisol and aldosterone [114], the teleostean MR demonstrated ligand promiscuity *in vitro* by binding cortisol, aldosterone, 11-deoxycorticosterone, corticosterone, and 11-deoxycortisol (see references in Table 2). Both 11-deoxycorticosterone and cortisol have been shown to signal through MR in teleosts (reviewed in [115]). However, the nature of the real physiological MR ligand and its functions is still a matter of debate [9,68,72,73] and ongoing research [116–118].

The nuclear progesterone receptor (PR) has been described up to now only as a single gene in teleost fishes; the duplicated copy seems to be lost. Interestingly, the PR was characterized very thoroughly in a few model species like zebrafish, medaka, Atlantic salmon, Atlantic cod, and fathead minnow, and was found to be activated by DHP, 20β-S, progesterone, and in some cases 17α-hydroxyprogesterone (see Table 2). Recently, the existence of four different splicing variants of the *pgr* gene in gilthead seabream was demonstrated, which raises the possibility for dominant negative transcriptional regulation [119]. Whether the existence of splice variants of the *pgr* gene are a common feature of teleost fishes awaits deeper investigation.

Together with the estrogen receptor (ER), the androgen receptor (AR) ranges among the best characterized nuclear receptors in teleost fishes. Similar to the GR, the AR gene is duplicated in most teleost fish species analyzed to date (Table 2). The genes are named AR1 and AR2 in pejerrey [120], ARa and ARb in Nile tilapia [106], and ARα and ARβ in medaka [121], plainfin midshipman [122], and rainbow trout [123]. The ARβ subtype was secondarily lost in cypriniformes like zebrafish [76,124] and fathead minnow [110,125]. Only for one species out of all teleost species, the three-spined stickleback, splice variants of the ARβ gene (ARβ1 and ARβ2) were reported [77]. The relevance and function of these splice variants were not described in detail. Thus, the physiological implications of these two splice variants need further investigation. Up to now, all characterized AR subtypes were described to bind several androgens like 11-KT, T, 11β-hydroxytestosterone, DHT, and androstenedione (see Table 2 for references). In transactivation studies, 11-KT was found to be the most efficient androgen

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Table 2
Evidence for mRNA expression and ligand binding for steroid receptors in teleost fish species.

Receptor (gene)	mRNA detected			Ligand binding		Gene only annotated in species*
	Species	Gene (splice variants)	Reference	Confirmed ligand	References	
GR (*nr3c1*)	*Cyprinus carpio*	GR1, GR2	[105]	Cortisol	[105]	*Esox lucius*, *Neolamprologus brichardi*, *Larimichthys crocea*, *Cynoglossus semilaevis*, *Notothenia coriiceps*, *Stegastes partitus*, *Maylandia zebra*, *Astyanax mexicanus*, *Poecilia formosa*, *Takifugu rubripes*, *Oryzias latipes*, *Poecilia reticulata*, *Xiphophorus maculatus*, *Pundamilia nyererei*
	Salmo salar	GR	[335]			
	Danio rerio	GR (GRα, GRβ)	[108,139,309,310]	Cortisol	[108,336]	
	Porichthys notatus	GR1, GR2	[122]			
	Odontesthes bonariensis	GR1, GR2	[120]			
	Gadus morhua	GR1	[109]			
	Pimephales promelas	GR	[110]			
	Haplochromis burtoni	GR1, GR2	[113]	Cortisol, aldosterone	[113]	
	Oreochromis niloticus	GR1, GR2 (GR2a/b)	[106]			
	Onchorhynchus mykiss	GR1, GR2	[107,112,337]	Cortisol, cortisone	[107,112]	
MR (*nr3c2*)	*Cyprinus carpio*	MR	[105]	Cortisol, aldosterone, 11-deoxycorticosterone	[105]	*Esox lucius*, *Maylandia zebra*, *Notothenia coriiceps*, *Larimichthys crocea*, *Poecilia reticulata*, *Cynoglossus semilaevis*, *Stegastes partitus*, *Poecilia formosa*, *Astyanax mexicanus*, *Xiphophorus maculatus*, *Pundamilia nyererei*, *Takifugu rubripes*, *Oreochromis niloticus*, *Oryzias latipes*, *Neolamprologus brichardi*
	Salmo salar	MR	[335]			
	Danio rerio	MR	[139,309]	Cortisol, aldosterone, 11-deoxycorticosterone	[64,336]	
	Onchorhynchus mykiss	MR (MRa, MRb)	[65]	Aldosterone, 11-deoxycorticosterone, corticosterone, 11-deoxycortisol, cortisol	[65]	
	Haplochromis burtoni	MR	[113]	Cortisol, aldosterone	[113]	
PR (*nr3c3*, *pgr*)	*Danio rerio*	PR	[139,167,200,338,339]	17α,20β-Dihydroxy-4-pregnen-3-one, 17α,20β,21-trihydroxy-4-pregnen-3-one, progesterone, 17α-hydroxyprogesterone	[167,338]	*Stegastes partitus*, *Oreochromis niloticus*, *Notothenia coriiceps*, *Larimichthys crocea*, *Poecilia reticulata*, *Cynoglossus semilaevis*, *Haplochromis burtoni*, *Pundamilia nyererei*, *Esox lucius*, *Poecilia formosa*, *Astyanax mexicanus*, *Xiphophorus maculatus*, *Maylandia zebra*
	Salmo salar	PR	[340]	17α,20β-Dihydroxy-4-pregnen-3-one, 17α,20β,21-trihydroxy-4-pregnen-3-one	[340]	
	Oryzias latipes	PR	[341]	17α,20β-Dihydroxy-4-pregnen-3-one, 17α,20β,21-trihydroxy-4-pregnen-3-one, progesterone	[341]	
	Gadus morhua	PR	[342]	17α,20β-Dihydroxy-4-pregnen-3-one, 17α,20β,21-trihydroxy-4-pregnen-3-one, progesterone, 17α-hydroxyprogesterone	[342]	
	Sparus aurata	PR (pgr_tv1, pgr_tv2, pgr_tv3, pgr_tv4)	[119]	17α,20β-Dihydroxy-4-pregnen-3-one, 17α,20β,21-trihydroxy-4-pregnen-3-one, progesterone, 17α-hydroxyprogesterone	[119]	
	Pimephales promelas	PR	[125,230]	17α,20β-Dihydroxy-4-pregnen-3-one, 17α,20β,21-trihydroxy-4-pregnen-3-one, progesterone	[230]	
AR (*nr3c4*)	*Danio rerio*	AR	[76,127,139,200,323,343]	Testosterone, 11-ketotestosterone, 5α-dihydrotestosterone, 11β-hydroxytestosterone, androstenedione	[76,127,344]	*Stegastes partitus*, *Larimichthys crocea*, *Haplochromis burtoni*, *Esox lucius*, *Poecilia reticulata*, *Cynoglossus semilaevis*, *Poecilia formosa*, *Astyanax mexicanus*, *Salmo salar*, *Xiphophorus maculatus*, *Pundamilia nyererei*, *Maylandia zebra*, *Neolamprologus brichardi*, *Takifugu rubripes*
	Porichthys notatus	ARα, ARβ	[122]			
	Odontesthes bonariensis	AR1, AR2	[120,170]			

Table 2 (*continued*)

Receptor (gene)	mRNA detected			Ligand binding		Gene only annotated in species*
	Species	Gene (splice variants)	Reference	Confirmed ligand	References	
	Anguilla japonica	AR1, AR2	[126]	5α-Dihydrotestosterone, 11-ketotestosterone, testosterone, 11β-hydroxytestosterone	[126]	
	Pimephales promelas	AR	[110,125,318]			
	Gasterosteus aculeatus	ARβ (ARβ1, ARβ2)	[77]	11-Ketotestosterone, 5α-dihydrotestosterone	[77]	
	Oryzias latipes	ARα, ARβ	[54,121,208]			
	Dicentrarchus labrax	ARβ	[315]			
	Oreochromis niloticus	ARa, ARb	[106]			
	Onchorhynchus mykiss	ARα, ARβ	[123]			
	Micropogonias undulatus	AR1, AR2		Testosterone, 5α-dihydrotestosterone, 11β-hydroxytestosterone	[345]	
ER (*nr3a1*, ERα, *esr1*)(*nr3a2*, ERβ, *esr2*)	*Danio rerio*	ERα, ERβ (ERβ1, ERβ2)	[131,139,200,346–349]	Estradiol, estrone	[131,132,346,349]	ERα: *Poecilia reticulata*, *Cynoglossus semilaevis*, *Esox lucius*, *Larimichthys crocea*, *Poecilia formosa*, *Astyanax mexicanus*, *Gasterosteus aculeatus*, *Neolamprologus brichardi*, *Haplochromis burtoni*, *Xiphophorus maculatus*, *Pundamilia nyererei*, *Maylandia zebra*, *Stegastes partitus*, *Notothenia coriiceps* ERβ: *Esox lucius*, *Notothenia coriiceps*, *Cynoglossus semilaevis*, *Astyanax mexicanus*, *Poecilia reticulata*, *Haplochromis burtoni*, *Maylandia zebra*, *Neolamprologus brichardi*, *Pundamilia nyererei*, *Takifugu rubripes*, *Larimichthys crocea*, *Stegastes partitus*, *Poecilia formosa*, *Xiphophorus maculatus*
	Carassius auratus	ERβ	[350]			
	Pimephales promelas	ERα, ERβ (ERβ1, ERβ2)	[110,125,130]			
	Porichthys notatus	ERα, ERβ (ERβ1, ERβ2)	[160]			
	Fundulus heteroclitus	ERα	[222]			
	Oryzias latipes	ERα, ERβ (ERβ1, ERβ2)	[54,121,208,351]			
	Dicentrarchus labrax	ERα, ERβ	[315]			
	Onchorhynchus mykiss	ERα (ERα1, ERα2), ERβ (ERβ1, ERβ2)	[128,129]			
	Odontesthes bonariensis	ER1, ER2	[170]			
	Oreochromis niloticus	ERα, ERβ (ERβ1, ERβ2)	[106,352]	Estradiol	[352]	
	Salmo salar	ERα, ERβ	[353]	Estradiol	[354]	
	Gobiocypris rarus	ERα, ERβ (ERβ1, ERβ2)	[355]			
	Ictalurus punctatus	ERα, ERβ	[133,134]	Estradiol, estrone	[133,134]	
GPER-1 (*gper*, *gpr30*)	*Danio rerio*	GPER-1	[136,356–358]	Estradiol	[136]	*Esox lucius*, *Poecilia reticulata*, *Cynoglossus semilaevis*, *Stegastes partitus*, *Poecilia formosa*, *Astyanax mexicanus*, *Neolamprologus brichardi*, *Haplochromis burtoni*, *Oreochromis niloticus*, *Notothenia coriiceps*, *Larimichthys crocea*, *Xiphophorus maculatus*, *Pundamilia nyererei*, *Maylandia zebra*, *Oryzias latipes*, *Takifugu rubripes*
	Cyprinus carpio	GPER	[359]			
	Sparus aurata	GPER	[360]			
	Micropogonias undulatus	GPER	[137]	Estradiol	[137]	
mPR (mPRα, *paqr7*) (mPRβ, *paqr8*) (mPRγ, *paqr5*)	*Danio rerio*	mPRα, mPRβ	[138,139,361]	17α,20β-Dihydroxy-4-pregnen-3-one	[362]	mPRα: *Takifugu rubripes* mPRβ: *Larimichthys crocea*, *Poecilia reticulata*, *Stegastes partitus*, *Astyanax mexicanuss* mPRγ: *Esox lucius*, *Notothenia coriiceps*, *Larimichthys crocea*, *Poecilia reticulata*, *Stegastes partitus*
	Ictalurus punctatus	mPRα, mPRβ, mPRγ	[138,140]			
	Pimephales promelas	mPRα, mPRβ, mPRγ	[37,125]			

(*continued on next page*)

Table 2 (*continued*)

Receptor (gene)	mRNA detected			Ligand binding		Gene only annotated in species*
	Species	Gene (splice variants)	Reference	Confirmed ligand	References	
	Salvelinus alpinus			17α,20β-Dihydroxy-4-pregnen-3-one	[363]	
	Onchorhynchus mykiss	mPRβ	[364]			
	Micropogonias undulatus	mPRα		17α,20β,21-Trihydroxy-4-pregnen-3-one	[227,365]	
	Carassius auratus	mPRα, mPRβ, mPRγ1, mPRγ2	[141,142]	17α,20β-Dihydroxy-4-pregnen-3-one	[141]	
	Cynoscion nebulosus	mPR	[366]	Progesterone	[366]	
mAR (*zip9*)	*Micropogonias undulatus*	zip9	[144]	Testosterone, 11-ketotestosterone, 5α-dihydrotestosterone	[143,144]	*Danio rerio*, *Ictalurus punctatus*, *Esox lucius*, *Larimichthys crocea*, *Poecilia reticulata*, *Cynoglossus semilaevis*, *Stegastes partitus*, *Poecilia formosa*, *Astyanax mexicanus*, *Neolamprologus brichardi*, *Haplochromis burtoni*, *Xiphophorus maculatus*, *Pundamilia nyererei*, *Maylandia zebra*, *Oryzias latipes*, *Takifugu rubripes*, *Oreochromis niloticus*

The list of references in this table is not exhaustive.

Abbreviations: GR, glucocorticoid receptor; MR, mineralocorticoid receptor; PR, progesterone receptor; AR, androgen receptor; ER, estrogen receptor, GPER, G protein coupled estrogen receptor; mPR, membrane bound progestin receptor; mAR, membrane bound androgen receptor.

* The entries in this column were derived from a search in the GENE database of the NCBI in February 2015.

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[76,77,126,127] and was therefore considered to be the physiological ligand of the teleostean AR. DHT, the ligand of the human AR, was until recently considered to be non-existent in teleost fishes. However, since DHT was lately detected in the plasma of fathead minnow [84], the question if 11-KT is the only physiological ligand of the teleost AR needs further clarification.

As already outlined in the previous chapter, the aromatase is the best characterized enzyme among the steroidogenic enzymes due to its key role in hormonal control of sexual development in teleost fishes. Additionally, the estrogen receptor is the best characterized nuclear receptor in teleost fishes, because this receptor mediates the effects of estradiol, the product of the aromatase. The ER has been identified in a large variety of teleost species (Table 2) and the published information points to a duplicated gene (ERα or *esr1* and ERβ or *esr2*) in all fish species analyzed to date. The rainbow trout is so far the only fish, where each subtype has two splice variants, namely ERα1 (*esr1a*), ERα2 (*esr1b*), ERβ1 (*esr2a*), and ERβ2 (*esr2b*) [128,129]. In most fish species, two splice variants for ERβ were detected (Table 2). Sometimes, one of these splice variants was erroneously named ERγ [106,110,130]. All ER subtypes and isoforms from teleost fishes, which have been characterized up to now, can be activated by estradiol (see references in Table 2) and in some cases estrone, albeit slightly weaker [131–134]. The different ER subtypes and isoforms have diverging expression patterns (see references in Table 2), which might indicate tissue- and developmental stage-specific roles for the ER in teleost fishes.

Beside the classical nuclear steroid hormone receptors, membrane bound steroid receptors were found in teleost fishes as well as in humans [103,135]. These receptors are mostly G protein coupled receptors, which exert their non-genomic actions through rapid, intracellular signaling mediated by second messengers like cAMP or the MAP kinase pathway [103]. In teleost fishes, one member of this group is the G protein coupled estrogen receptor GPER-1. This gene has been detected in zebrafish, common carp, gilthead seabream, and Atlantic croaker (see Table 2 for references). Up to now, no information about the duplication of the gene is reported. GPER-1 was found to bind estradiol with a similar affinity as the human ortholog GPR30 [135–137]. GPER-1 is annotated in a large number of other fish species, but awaits further characterization in these animals (Table 2).

Slightly better characterized than the membrane bound estrogen receptors is the family of membrane progestin receptors (mPRs) of teleost fishes (Table 2). The mPRs have been detected in more fish species than the GPER-1, and in addition, the ligand binding abilities of the mPRs have been determined in a variety of fish species (see references in Table 2). However, the exact number of genes coding for mPRs in teleost fishes is not yet clearly established. In zebrafish, only two subtypes are known (mPRα and mPRβ [138,139]), while in the channel catfish, the fathead minnow, and the goldfish three forms are described (mPRα, mPRβ, and mPRγ [125,140–142]). mPRα and mPRβ seem to have originated from genome duplication, as these genes are closer related to themselves than to mPRγ [140]. Besides, it might be possible that a duplicated gene of mPRγ exists, since in goldfish two mPRγ isoforms have been reported [141]. It is not yet clear, whether goldfish mPRγ1 and mPRγ2 are splice variants originating from one gene, or subtypes originating from two different, albeit closely related genes. Whatever the evolutionary background for the variety of mPR genes might be, those mPRs which have been characterized regarding ligand binding were found to bind DHP, 20β-S, and progesterone (see references in Table 2).

The least characterized member of the membrane bound steroid hormone receptors is the membrane androgen receptor (mAR). Evidence for the existence of the mAR has been published and reviewed [103,143]; however, the gene has been so far only cloned from the Atlantic croaker and described to be similar to the zinc transporter ZIP9 [144]. ZIP9 has been annotated in a variety of other teleost fish species (Table 2); however, it was never related to steroid signaling, but so far only characterized in regard to its role in zinc homeostasis, as for instance in zebrafish [145,146]. Recombinantly expressed ZIP9 from the Atlantic croaker was found to bind T with high affinity and high specificity [144]. However, whether ZIP9 of other teleost fish species is acting as membrane androgen receptor needs further elucidation.

Steroid hormone receptors, both nuclear and membrane bound forms, are very well conserved between teleost fishes and humans. The gene structure, their chromosomal location, and the deduced protein sequence are largely comparable [20]. Naturally, the gene duplication in teleost fishes represent a major difference to the human system and the existence of duplicated receptors opens the possibility for diverse regulatory processes like tissue- or developmental stage-specific effects. Nevertheless, the genes of the receptor classes are highly homologous to each other and the receptors bind the same ligands, although the PR, AR, and MR from teleost fishes prefer other ligands than the human orthologs as outlined above. In a few cases, even splice variants exerting dominant negative effects on the respective canonical receptor were described in teleost fishes. In humans, splice variants of nuclear receptors are very common [147], and the research regarding this aspect in teleost fishes is lagging behind. Besides, further differences between human and teleost steroid hormone receptors with respect to ligand specificities, ligand binding and dissociation kinetics, posttranslational modifications, usage of corepressors or coactivators, and regulation of transcriptional activation or repression between human and teleost steroid hormone receptors are certain to exist, but are not reviewed here.

4. Physiological roles of steroid hormones in teleost fishes

In both fishes and humans, steroid hormones are involved in a plethora of processes like embryonic development, sex determination and differentiation, metabolism, immune responses, osmoregulation, circadian rhythms, mating, reproduction, and behavior. No matter which physiological process is considered, usually many different steroid hormones are involved in the regulation. Only in a few cases isolated effects can be ascribed to the action of a single steroid hormone. Examples are the prevention of further ovulations during pregnancy in humans by progesterone [63] or the stimulation of vitellogenin synthesis in the liver of teleost fishes by estradiol [75]. Furthermore, steroid hormones cannot only influence in feedback mechanisms their own endocrine axes, but can also interact with other endocrine axes [35]. The hypothalamus–pituitary–interrenal axis controls primarily stress and immune responses, while the hypothalamus–pituitary–gonadal axis controls reproduction [9]. However, the stress hormone cortisol can interfere with the reproductive signaling by accelerating, delaying, or completely inhibiting reproduction [59,148–150]. Inversely, sex steroids can influence the stress response [151]. To disentangle the complete steroid hormone network of teleost fishes in all aforementioned single processes would lead beyond the scope of this review. Therefore, we will focus on a few steroid hormone related aspects of fish physiology, which are most dissimilar to the human system, namely reproduction, sex differentiation, pheromone signaling, and osmoregulation. Since these processes are either very well known or not relevant at all in humans, we mostly refrain from a direct comparison of the fish physiology to the human situation.

4.1. Reproduction

Teleost fishes have evolved a tremendous diversity of reproductive strategies for adaptation to a large variety of aquatic

environments [32]. These strategies can range from collective pelagic spawning without any egg care (e.g., Atlantic cod), over spawning in gravel holes excavated by tail movements (e.g., rainbow trout) and spawning within sheltered cavities with parental care (e.g., channel catfish), to spawning in a nest and protecting the eggs by taking them into the mouth of the female (e.g., Nile tilapia) [32]. Further, the fish reproduction has been adapted to the respective aquatic conditions, which become apparent as different reproductive cycles (e.g., seasonal reproduction once a year like for rainbow trout, monthly reproduction like for Nile tilapia, or daily reproduction like for medaka) [32]. Naturally, different reproductive cycles entail diverging steroid hormone rhythms; however, certain regulatory processes are conserved among teleost fishes. These include the hypothalamus–pituitary–gonadal axis, the major regulatory cascade which is well conserved not only in teleost fishes, but in all vertebrates [152]. Inside the cascade, the pituitary hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are central and control the downstream processes like steroid hormone synthesis [75,153,154].

In females, the reproductive cycle is dominated by estradiol in the early phase, i.e. growth of oocytes, and by the maturation inducing steroid (MIS) in the late phase, i.e. oocyte maturation prior to ovulation [31,155,156]. During oocyte growth, the pituitary hormone FSH stimulates the follicular cells to secrete estradiol into the circulation, which in turn stimulates the synthesis of vitellogenin in the liver [31,74,75,153]. Vitellogenin, a glycolipophosphoprotein, is transported into the growing oocyte by pinocytosis [31,32] and serves as nutritional provision for the developing embryo [155,157]. After completion of oocyte growth and vitellogenesis, estradiol levels are decreased due to down-regulation of ovarian aromatase (*cyp19a1a*) [31,153]. In salmonids, testosterone is synthesized by the thecal cells and subsequently aromatized to estradiol by the granulosa cells [31]. The rapid decline of estradiol levels might deprive the fully grown oocytes of their hormonal milieu, and it was hypothesized that testosterone may fill this void [31]. When estradiol concentrations drop due to down-regulation of aromatase, the up-regulation of *hsd20b* in the granulosa cells [153] stimulated by the pituitary hormone LH and the resulting synthesis of the MIS initiate the processes of oocyte maturation [75,153], which is a prerequisite for successful fertilization [158]. The substrate for Hsd20b, 17α-hydroxyprogesterone, is provided by the thecal cells, and the interaction of these two cell layers to produce the MIS has been termed as two-cell type model [75,158]. The MIS is either DHP or 20β-S; DHP was mostly found in salmoniformes, cypriniformes, cyprinodontiformes, siluriformes, beloniformes, esociformes, osteoglossiformes, and clupeiformes, while 20β-S is the MIS in many perciformes [74,75,159]. The MIS binds to mPRs [103], triggers intracellular signaling, and stimulates thereby all processes associated with oocyte maturation, e.g., germinal vesicle breakdown corresponding to the first meiotic cell division, spindle formation, chromosome condensation, and formation of the first polar body [75,155]. While the MIS stimulates oocyte maturation via non-genomic actions by mPRs, it was hypothesized that the MIS regulates ovulation by genomic mechanisms, thus utilizing a nuclear PR [75]. Ovulation is the release of mature oocytes from their follicles to the ovarian cavity, where the oocytes await oviposition [32].

Males of teleost fishes have developed different mating tactics, where males can be either bourgeois or sneakers [78,160,161]. Bourgeois males are normally larger, defend territories, display secondary sexual characteristics like breeding colors, and court females [78,160,161]. Sneaker males are usually smaller, younger, display less developed secondary sexual characteristics, and steal fertilizations by female mimicry [78,161]. In salmonids, the mating tactic is fixed, since sneaker males cannot develop into bourgeois males, while in African cichlids like Burton's mouthbrooder frequent transitions between both mating tactics have been observed [162]. Both types of males exhibit different concentrations of circulating androgens [78,161], and the effects of androgens on secondary sexual characteristics like color changes at maturation are known in many teleost fishes [78,163]. However, the general control of reproduction by steroid hormones is similar in both types of males. 11-KT display seasonal changes in plasma with increasing levels towards spawning maturation and peak levels at the onset of the spawning period [78]. In the testis, the pituitary hormone FSH stimulates 11-KT synthesis, which in turn induces spermatogenesis [78,154,163,164]. At the end of gametogenesis, 11-KT levels drop locally, and the synthesis of the MIS is increased [165,166] under the control of the pituitary hormone LH [154]. Similar to females, the MIS stimulates the maturation of spermatocytes by initiating meiotic cell divisions [165–167]. Furthermore, the MIS induces the production of seminal fluid by the efferent ducts and enhances the sperm motility by alteration of pH and fluidity of the seminal fluid [165,167]. Lastly, matured spermatozoa are released into the seminal fluid leading to the formation of milt, which is stored until spawning [166].

4.2. Sex differentiation

Teleost fishes display a tremendous plasticity in regard of sexual determination and subsequent gonadal differentiation [32–34,153]. Sexual determination refers to the genetic or environmental processes that define the gonadal fate, while the term sexual or gonadal differentiation is used for the transformation of the morphologically undifferentiated gonad into an ovary or a testis [33,34]. Sexual determination can be genetically controlled with either monogenic or polygenic systems or can be controlled by environmental factors like temperature, pH, or social cues [33,34]. Also, mixed control mechanisms with factors from both systems are possible [33,34]. Regarding sexual differentiation, the plasticity ranges from gonochorism to hermaphroditism. In gonochoristic species, individuals are either male or female [153], and the undifferentiated gonad develops directly into an ovary or into a testis [33,34]. Hermaphroditic species can be either synchronic or sequential. Synchronic species display testicular and ovarian components at the same time [33,34,153], while sequential species change their gender during their lifetime. Protogynous hermaphrodites develop first as females and change to males, while protoandrous hermaphrodites develop first as males and change later to females [33,34,153]. The underlying mechanisms of the sexual plasticity in teleost fishes have been extensively reviewed elsewhere [33,34].

Although teleost fishes show an enormous plasticity in concern of sexual determination and differentiation, the involvement of sex steroids, i.e., androgens and estrogens, is a common feature. The precise role of androgens and estrogens in the process is not totally clear until now; however, the fact that both hormones are essential for sex differentiation is undoubted. The hormones itself do not initiate the gonadal sex differentiation, but their timely appearance and sustainment are fundamental for the process [34,120]. The ratio of androgen to estrogen levels is important for sexual differentiation, where an excess of estradiol leads to females and an excess of 11-KT produces males [33,34]. In this regard, the enzyme aromatase (Cyp19a1a), which converts androgens into estrogens, is the key enzyme for the development of ovaries [33,34,95,168,169], and indeed, the expression of cyp19a1a was found to be specific for future females in a variety of teleost fish species ([33,95,168] and references therein). Estradiol is required not only for the differentiation, but also for the maintenance of the female phenotype [34,95,168,170]. While the differentiation of the female sex is not possible without estradiol, the presence of androgens is currently considered to be a consequence of the differentiation along the male pathway [34,120,168,170]. Nevertheless, androgens were

found to regulate the differentiation of the efferent duct system [76]. It is worth mention that although the involvement of androgens in male fish sex differentiation is well accepted, most of the published evidence is related to estrogens and only to a lesser extent to androgens ([170] and references therein).

The importance of androgens and estrogens for sex differentiation also becomes apparent when the action of these hormones is enhanced. In a certain, species-specific time window of the development, teleost fish larvae are extremely susceptible to exogenous androgens or estrogens. When fish larvae are exposed to exogenous androgens or estrogens in this critical time window, the gonadal fate is strongly directed into testis or ovary formation, respectively [34,76,120,170–172]. Strikingly, even in species with a strict genetic sex determination like the medaka, a reversal of genetic males to females by estrogens and genetic females to males by androgens can be induced [10,162]. Given the strong impact of the sex steroids on the gonadal fate, it is likely to expect that both hormone classes play vital roles in sequential hermaphrodites. While in many protoandrous species estradiol is highly associated with the gender change, the role of 11-KT is not yet clear, as there is evidence both for and against its involvement in sex change related processes (reviewed in [173]).

4.3. Pheromone signaling

Teleost fishes inhabit an environment which limits visual information, but supports olfactory cues like pheromones [174,175]. Pheromones are defined as substances (or mixture of substances) released by an individual and eliciting an adaptive, specific, and species-specific response in other individuals, that neither requires experience nor learning [174,176,177]. Fish commonly use pheromones to regulate a variety of functions, e.g., anti-predation and alarm cues, non-reproductive aggregation like kin recognition in hierarchies or formation of schools, and reproductive stimulations to synchronize gamete maturation and spawning interactions [161,177,178]. While the chemical identity for many pheromones is not yet known, reproductive pheromones, which are the best studied group of pheromones, include steroidal and non-steroidal substances [174,176,177]. Reproductive pheromones can be further subdivided into releaser and primer hormones, where the first directly stimulate a rapid response in recipients, and the latter induce physiological changes in recipients after a certain delay period [179]. Reproductive pheromones are mainly derived from gonadal steroid hormones, because their peak production is associated with critical reproductive events like ovulation and an imminent spawning opportunity [174]. Thus, these hormones have a dual function in both endogenous as well as exogenous regulation of reproduction [161,174,175,180]. Depending on the species, the reproductive pheromones can be either free steroids or steroids conjugated with glucuronides or sulfates [161,177,179]. Free steroids are usually poorly water soluble and were considered to have a low transmission range [179], while conjugation with glucuronic acid or sulfates increases their hydrophilicity significantly. The three types of steroids are released by the fish via three different routes: free steroids are released predominantly via the gills, glucuronidated steroids are removed through the bile, and sulfated steroids are excreted via the urine [181]. The nature, action, and physiological implications of fish pheromones in different species have been frequently and extensively reviewed [174–177], and therefore, we will only present a few examples for teleost fishes here.

With regard to reproductive pheromones, the goldfish is the best characterized member of the teleost fishes and it has been observed that the steroid release closely parallels the respective steroid plasma concentration [177]. Free steroids and conjugated steroids are released into the water [177]. After the female goldfishes finish vitellogenesis, they release androstenedione, which causes the males to show agonistic behavior. During oocyte maturation, the DHP released by the females exerts a primer effect on the males in terms of onset of steroidogenesis in the testis. At the onset of ovulation, females release sulfated DHP and the males start the following and chasing behavior as well as the milt production. Finally, the ovaries of the females produce the non-steroidal hormone prostaglandin F2a, which induces oviposition behavior. The release of prostaglandin F2a triggers the courtship and spawning behavior in males [161,165,174–176]. While the goldfish did respond to free steroids as well as to sulfated DHP, Burton's mouthbrooder did not react to free steroids, but exclusively to a variety of conjugated steroids, including conjugates of estrogens, androgens, and progestins [182]. However, the biological effects induced by the steroidal pheromones are not evaluated to date [174,175]. In zebrafish, even the identity of the reproductive pheromones is not yet completely clear. The females of zebrafish were shown to ovulate in the presence of male holding water and testis homogenates [179,180,183], while the males displayed courtship behavior upon exposure to ovarian extracts and were able to distinguish between ovulated and non-ovulated females [184]. The observed effects were abolished in both cases after β-glucuronidase treatment, which underlines the importance of glucuronidated molecules as reproductive hormones [180,184]. Surprisingly, more recent studies indicated that the zebrafish olfactory system (the system that is responsible for pheromone signal transduction) does not detect glucuronidated estradiol and testosterone, but reacts to prostaglandin F2a and sulfated DHP [174,185]. To clarify these controversial observations, further research is needed.

As can be seen from the outline above, the variety of teleost fish species utilize the same reproductive pheromones as signaling molecules. However, their species-specific use is believed to be ensured by several factors like the precise mixture of pheromones released, their longevity in the environment, the physiological and behavioral state of the receiving fish, other visual or acoustic cues, or a small active space [186].

4.4. Osmoregulation

In humans, the glucocorticoid action (i.e., cortisol via the GR regulating metabolism, inflammatory responses, and stress responses) and the mineralocorticoid action (i.e., aldosterone via the MR regulating ion resorption and water retention) are clearly distinguished processes [63]. Since the human MR can bind cortisol with higher affinity than aldosterone, the specificity of the MR action in the kidney is ensured by a strong expression of HSD11B2, removing excess cortisol [114]. The 11β-hydroxysteroid dehydrogenase type 2 catalyzes the conversion of cortisol to cortisone, which is unable to bind to the MR, and as such the enzyme controls the access of aldosterone to its receptor [114]. In teleost fishes, however, the distinction between glucocorticoid and mineralocorticoid actions is not that clear. This is due to the common opinion that cortisol carries out both glucocorticoid and mineralocorticoid function [59,72,115]. As already reviewed in chapter 3, the teleost GR binds exclusively cortisol, while the teleost MR can bind cortisol and 11-deoxycorticosterone (DOC) among other steroids (Table 2). DOC is present in significant concentrations in plasma of teleost fishes, albeit lower than cortisol [72], and DOC can induce transactivation by the MR, but not by the GR [115]. Therefore, it was postulated that DOC might be the physiological ligand of the MR in teleost fishes [65,66,68,73,105]. However, in regard of the classical mineralocorticoid action, i.e., the osmoregulation, both DOC and the MR seem to play only minor roles in teleost fishes [72,73,115,187]. In contrast, the important role of cortisol in osmoregulation is supported by a large body of experimental evidence (reviewed in [59,73,115,187]).

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The majority of teleost species is considered to be stenohaline, i.e., living either in fresh water or in seawater, while the remaining species are euryhaline and have the capability to adapt to large changes in salinity [187]. Among the euryhaline species are fishes which inhabit estuaries like killifish or which migrate between fresh water and seawater as part of their normal life cycle like Atlantic salmon. Since teleost fishes maintain their plasma osmotic concentration at one-third to that of seawater, they have to import ions against the gradient in fresh water and to release ions against the gradient in seawater [187]. In fresh water, cortisol interacts with prolactin and maintains the expression of ion transporters in the gills for the uptake of sodium and chloride ions [187]. Furthermore, cortisol stimulates the expression of the freshwater Na^+/K^+-ATPase isoform (NKAa1a) [66] and as a result, increases the uptake of sodium ions [188]. In seawater, cortisol and growth hormone/insulin-like growth factor I interact to control the epithelial transport capacity for secretion of sodium and chloride ions [187]. Here, cortisol was found to induce the expression of the seawater Na^+/K^+-ATPase isoform (NKAa1b) [66]. While cortisol displays a dual osmoregulatory function in both processes, the actions of growth hormone and prolactin are antagonistic [187]. In euryhaline species adapting to seawater, cortisol upregulates the Na^+/K^+-ATPase activity by enhancing the expression of NKAa1b, and the expression of the $Na^+/K^+/Cl^-$ cotransporter (NKCC) in the gills [115,189]. In the intestine, cortisol induces salt and water absorption to maintain internal water balance [190]. When euryhaline fish adapt to fresh water, cortisol upregulates the transcription of NKAa1a, and the uptake of sodium and chloride ions is generally increased [115,187]. The involvement of cortisol and the GR in the aforementioned processes has been underlined by studies demonstrating that the blockade of GR by the antagonist RU486 inhibits adaptation to differing salinity conditions [72,117,188,190]. However, the mechanisms by which cortisol affects different aspects of osmoregulation are complex and likely dependent on the species and the environmental condition analyzed [73,187,188]. Furthermore, electrochemical potentials play a key role in osmoregulation, since negative potentials were observed in tight fresh water gill epithelia and positive potentials in leaky sea water gill epithelia [66].

In conclusion, the osmoregulation in teleost fishes is controlled by cortisol and the GR (and other non-steroidal hormones) and not by the MR and its putative ligand DOC. Whether the MR has a distinct role in teleost fish physiology (an influence on the behavior was recently suggested [115]) and which ligand might trigger these functions, remains unclear up to now.

5. Environmental hazards: endocrine disruption

All aquatic animals and among them teleost fishes are exposed to a tremendous variety of compounds, which can be either natural or anthropogenic. A large number of structurally diverse substances have been shown to disrupt the function, the levels, and the distribution of endogenous hormones and are as such classified as endocrine disrupting chemicals (EDCs) [21,23,191]. EDCs enter the aquatic habitats by direct discharge to the water, i.e. sewage effluents or domestic and industrial discharge in less developed countries, by runoff of chemicals from agricultural land or feedlots, and by diffuse sources such as storm water runoff or floods [192]. EDCs can occur naturally in the environment, like for instance phytoestrogens, but those compounds with potentially the strongest disruption effects are derived from man-made chemicals. Furthermore, the amount of data regarding the impact of phytoestrogens on teleost fishes [193,194] is scarce compared to the overwhelming number of studies analyzing the impact of anthropogenic substances on teleost fishes ([21,23,192,193,195,196] and references therein). Anthropogenic EDCs include herbicides, fungicides, insecticides, chemical industry contaminants, ship antifouling agents, polychlorinated biphenyls (PCBs), phthalate plasticizers, personal care products, and pharmaceuticals for the treatment of human diseases [192,197,198]. Among the last group, many steroidal hormones derived from human contraceptives or anabolic growth promotors for livestock can be found [21,192,199–201].

Among the natural and anthropogenic EDCs, substances disrupting the steroid hormone regulation can be designated as xenosteroids [202,203], with further subclasses of xenoestrogens or xenoandrogens [204,205]. EDCs exert their effects at every level of steroid hormone regulation, because they can interfere with the hypothalamus–pituitary–gonadal and interrenal axis [206–211], steroidogenesis [110,191,212–215], steroid transport [203,216,217], steroid catabolism [196,218], and with the hormone receptor binding [21,110,191]. Here, the compounds can have an estrogenic or androgenic effect depending on the respective receptor they bind to, and by binding to the receptor can trigger the activation or repression of ER- or AR-responsive genes [21,219]. The compounds can also exert anti-estrogenic or anti-androgenic effects by binding competitively to the ER or AR, respectively, and block the receptor for the endogenous hormone, thus inhibiting the transcriptional activity [21,110,219]. Furthermore, certain substances can exert (anti-)estrogenic and (anti-)androgenic effects without interacting with a receptor, but by influencing expression and activity of, for example, aromatase (Cyp19a1) [50,191,193,220], or other steroidogenic enzymes [221,222]. Additionally, EDCs can impact the expression of the steroid hormone receptors [223–225]. The very number of terms and definitions regarding estrogen and androgen signaling disruption indicates already that this part of endocrine disruption research has been and is still extensively investigated due to the ubiquity of estrogenic and androgenic compounds and their dramatic effects on sexual differentiation, sex reversal, and skewed sex ratios [21,191,196,221,226]. Research on the disturbance of other steroid signaling pathways is not completely neglected, but only lagging behind the amount of studies concerning estrogen and androgen pathway disruptions. However, in the last decade, several studies focusing on the analysis of interferences with progestin signaling [21,200,227–230] and corticosteroid signaling [21,150,207,231,232] by EDCs were published.

Since endogenous steroid hormones are involved in the regulation of many different processes, the interference with these regulatory pathways by EDCs affects virtually every aspect of fish physiology not only in adults, but also in developing fish fry [129,228,233,234]. The two processes mostly analyzed in adult fishes in connection with EDCs are reproduction and sexuality; however, it has to be considered that processes altering sexuality also influence reproduction. In regard to teleost fish reproduction, several aspects have been found to be strongly affected: spawning and fecundity in both sexes [21,110,196,209,219,221,235,236], maturation of gametes in both sexes [21,110,237], reduced ovarian growth in females [110], and induction or repression of vitellogenin synthesis (depending on the compound) in both sexes [215,219,238,239]. Concerning sexuality, EDCs interfere with the gonadal differentiation [110,196,209,215,238–240], gonad histopathology [21,191,241–243], induction of intersexuality [110,199,219,233,235,238,239], feminization of male fishes [110,239,244,245], masculinization of female fishes [199,246–248], and often induce skewed ratios of females to males [110,199,219,233,235,238,239]. Further, EDCs modulate not only the sexual behavior of the fishes [194,195,240], but also aggression, anxiety, play behavior, attention, learning, and memory [235,239,249]. Last but not least, EDCs can attenuate, suppress or enhance the corticosteroid response [21], and can entail developmental alterations in fish fry [233,234]. The above list of endocrine disrupting effects is only intended for an overview of endocrine

disruption processes. For further information, the interested reader is referred to the cited literature.

The magnitude of a certain endocrine disrupting effect is dependent on a variety of variables like the species, life stage and duration of EDC exposure, as well as concentration, mode of action, and potency of EDCs or EDC mixtures [239,241,246–248,250,251]. Endocrine disrupting effects seem to be reversible or permanent; however, the observed effects are highly dependent on the study design and the investigated endpoint. It can thus happen that a similar exposure is described as being reversible, as well as being permanent. In zebrafish for instance, the induction of vitellogenin expression was found to be reversible in one study [238], but persistent in another study [250]. The differing observations can be explained by a 3 week exposure with 3–5 months depuration [238] versus a full life cycle exposure with 3 months depuration [250]. Also, the effects of estrogens on the sexual differentiation in zebrafish were considered to be completely irreversible [238,241,250], but other studies found the effects to be partly reversible [239,252,253]. Therefore, even the reversibility of a certain endocrine disrupting effect is probably dependent on several factors like the exposure concentration, exposure duration, life stage of exposure, recovery time, and the investigated endpoint [239,241,250,252], indicating that the interpretation and comparison of observed effects is problematic.

The research on endocrine disruption is largely performed using a few model fish species, like zebrafish [21,23,242,254,255], fathead minnow [21,242], medaka [21,208,242,255], and three-spined stickleback [21,256]. These model fish species offer several practical advantages like a small size, the ease of husbandry, a rapid life cycle, a high fecundity, and the availability of a large number of genetic tools [21,257,258]. In contrast, many wild fish species are long lived and need up to two years prior to the first spawning [257]. Here, rainbow trout represents a better model fish species [232,257,259], although disadvantages like the need for large fish facilities has to be considered. However, the different biology of wild fish species compared to the model species entails challenges in regard of the extrapolation of laboratory data to wild fishes, the population modeling, and the interpretation of effects data [257,260]. The prediction of endocrine disrupting effects in wild fish populations is further complicated, because the compounds often occur in mixtures in polluted environments [35]. The cocktail effect, which refers to mixtures of chemicals that can exert synergistic or antagonistic effects compared to the single compound(s), can lead to both over- and underestimation of the effect of a single substance [251].

6. Conclusions

As pointed out in this review, the research on steroid metabolism and action in teleost fishes is a central aspect, because steroid hormones are involved in the control of embryonic development, growth, metabolism, sex differentiation, immune responses, osmoregulation, and reproduction, thus influencing the fish's physiology during all stages of life. Supportive knowledge in the areas of steroidogenesis, steroid hormone receptors, and steroid hormone functions summarized over all teleost fishes is already large. However, teleost fishes, whether wild or cultivated, are notably sensitive to endocrine disrupting chemicals and bathed constantly in a medium containing a dilution of different pollutants [260], which can accumulate in the animals [221] and finally end up in the diet of humans. As the EDCs were shown to have adverse effects on human endocrinology [216], this aspect has to be thoroughly investigated. Here, small model species of teleost fishes like zebrafish or fathead minnow can serve as sentinel organisms to detect even trace amounts of endocrine disrupting compounds [255,261–263].

Regarding research on vertebrate development in general and endocrine disruption in particular, teleost fishes represent excellent model organisms. The high degree of conservation of the endocrine system of teleost fishes compared to humans [9,10,20], the possibility to phenocopy human diseases [8,264], and the practical advantages of small fish species [10,12,21] promote the usage of teleost fishes as model organisms. However, extensive knowledge of the biological characteristics of a certain species is an important pre-requisite for using this species successfully as model organism [23], for instance in endocrine disruption studies. In this light, we noticed that the current knowledge on steroid hormone related fish physiology, albeit being quite extensive, is not yet complete. The synthesis of steroid hormones is well understood if summarized over all teleost species, but for single species, the knowledge is rather scarce. Although the existence and the impact of duplicated genes responsible for steroid biosynthesis are known in a few species for single genes, the complete picture is far from being clear. The same holds true for the duplicated steroid hormone receptor genes and their splice variants, where further effort is needed to unveil the complex regulatory networks. The physiological roles of steroid hormones in fish reproduction, sex differentiation, and osmoregulation are reasonably well understood; however, a few fish-specific aspects (e.g., the function of the mineralocorticoid receptor and the identity of its natural ligand) are not yet conclusively resolved.

Nevertheless, we believe that the ongoing and the future research will address the mentioned gaps of knowledge and will extend our understanding of the basic biology of teleost fishes. This will in turn lead to a better understanding of human development and physiology, of endocrine disruption in humans, and hopefully will entail a responsible and sustainable handling of the environment, of which both humans and teleost fishes will benefit.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.steroids.2015.06.011.

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