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Dopamine system in the fish brain: A review on current knowledge

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Abstract
In fish, neuroendocrine system is the reciprocal crosstalk between the neurotransmitter/neuropeptides and endocrine factors. As in mammals, various neuroendocrine factors in fish are involved to regulate the fish physiology specifically reproduction and development. Dopamine is a key brain regulator that regulates fish reproduction and stress through a conserve neuronal pathway. Sex specific and reproductive stage related expression of dopamine probably is controlled by environmental factors as well as fish endogenous signals. D1 and D2 receptor families mediate the regulatory functions of dopamine neurotransmission, which regulates a range of brain activities. Recent study revealed the nine receptor subtypes of dopaminergic system and D1 receptor family, but not D2 family, is involved in the regulation of sex steroid production. Although dopamine localization and its mechanism appear to be conserved among vertebrates, major physiological differences between vertebrate classes and the diversity of fish, in particular in regard to site of synthesis, role of dopamine receptors, its signaling action and crosstalk with other neuropeptides, suggest the existence of species-specific regulating mechanisms in fishes. Based on the most recent research, this review gives a current update of the dopaminergic system and its mechanism of action within the framework of fish brain.

Keywords: Dopaminergic system, sex steroid, teleost, Dopamine receptors, fish reproduction

Introduction
The majority of fishes breed at a particular time of the year and the seasonal reproductive cycle is precisely maintained by neuroendocrine agents from the brain. In fish, neuroendocrine system is the reciprocal crosstalk between the neurotransmitter/neuropeptides and endocrine factors. These factors involved in the communication and induce the variety of physiological activity such as feeding, stress, social behavior and reproduction (Nardocci *et al*., 2014) [32]. In aquaculture practices, the stimulatory mechanism of gonadotropin-releasing hormone (GnRH) and involvement of inhibitory actions of dopamine has major implications (Bryant *et al*., 2016) [7]. Dual role of GnRH and dopamine (DA) in the neuroendocrine control of reproduction has been demonstrated in various, but not all, fishes, where DA participates in an inhibitory role and regulate last process gametogenesis such as final oocyte maturation, ovulation in females, and spermiation in males (Fontaine *et al*., 2013) [18]. In fishes dopamine activity in the brain varies with development and reproductive cycle and probably is controlled by environmental cues as well as endogenous signals (Dufour *et al*., 2010) [55]. It is reported that dopaminergic system influenced by the sex hormones in several teleost and changes both DA release and DA-D2 receptor level. Furthermore, it is documented that peripheral sex hormones target the dopaminergic hypophysiotropic system, as well as the other components of the brain-pituitary gonadotrophic axis, along with GnRH and gonadotrophins (Dufour *et al*., 2010) [55]. Various neuroanatomical investigations have shown that DA neurons in the preoptic area projected directly to the region of the pituitary and responsible for the inhibitory control of reproduction (Dufour *et al*., 2010; Kumar *et al*., 2014) [55, 24]. Similarly effect of DA and its receptor activators also exerts their inhibitory effect on the pituitary cells in fishes are well reported. Dopamine inhibits luteinizing hormone synthesis and demonstrated a role for DA in the control of LH and puberty in a juvenile European eel (Vidal *et al*., 2004) [51]. Moreover, DA stimulated GH release from perfused pituitary fragments of goldfish in a dose-dependent manner and functions as a GH-releasing factor (Anderson *et al*., 1993) [1]. Considerable reports have shown that numerous neurotransmitters that characterize specific brain systems interact

with the dopamine and involved to modulate neuroendocrine activity to regulate reproduction. Brain lesioning studies on goldfish demonstrated the presence of a GtH release-inhibitory factor (GRIF). Dopamine has GRIF like activity in goldfish and common carp to modulate the actions of LH-RH and spontaneous release of GtH (Peter, 1983) [34].

Previously, a review in 2010 discussed the neuroendocrine activity of dopamine in teleost reproduction (Dufour *et al*., 2010) [55]. Since last decades various experimental studies added the involvement of dopamine in the fish reproduction. In addition, dopamine regulated neuro-degenerative disorder associated gene expressions were also reported in fish model systems (Popesku *et al*., 2012) [40]. However recent updates on the dopamine system in fish brain are not discussed in a single document. Hence attempt has been made to convey the updates on dopamine in the brain of fishes. Abundant orexinergic fibers and terminals have been observed interspersed with the TH-ir cells of the POA and hypothalamus in the *L.* oculatus (Lozano *et al*., 2018) [28] suggests the collective role of peptides in the reproduction. Super fused POA slices treated with a NPY Y_2-receptor agonist, NPY 13-36 resulted in a significant reduction in TH-immunoreactivity in NPPa and demonstrated that DA and NPY interacts in NPPa to regulate the LH release (Kumar *et al*., 2014) [24]. Differences in regenerative capacity of the groups of dopaminergic neuronal populations in the adult zebrafish brain were also recently mentioned (Caldwell *et al*., 2019) [9]. Kiss pep tin receptors and TH and NPY expressing cells were colocalized in the POA and SCN in the brain of sea bass (Escobar *et al*., 2013) [17] and suggest the role of kiss pep tins to regulate a wide range of neuronal systems in the fishes. Present article discussing the current data on neuroanatomical updates of dopamine and its mechanism to influence the neuroendocrine and reproductive physiology in the fishes.

Dopamine synthesis and its metabolism

A catecholamine neurotransmitter dopamine (DA, a contraction of 3, 4-dihydroxyphenethylamine) is an organic chemical, an amine synthesized by removing a carboxyl group from a molecule of its precursor, L-DOPA, which is synthesized in the brain and kidneys. Tyrosine hydroxylase (TH) converts tyrosine (non-essential amino acid) to dihydroxyphenylalanine (L-DOPA; Musacchio *et al*., 2013) [31]. Dopamine is synthesized in a restricted set of cell types, mainly neurons in the brain and cells in the medulla of the adrenal glands (Seeman P, 2009) [47]. The primary process of metabolic pathway which includes transformation of metabolites and involvement of enzymes:

Primary: L-Phenylalanine → L-Tyrosine → L-DOPA → Dopamine (Wasel and Freeman, 2020) [54].

In addition to this dopamine also synthesize with other minor pathways are,

Minor: L-Phenylalanine → L-Tyrosine → p-Tyra mine → Dopamine

Minor: L-Phenylalanine → m-Tyrosine → m-Tyra mine → Dopamine.

Musacchio *et al*., 2013 [31] mentioned that, L-Phenylalanine is converted into L-tyrosine by the enzyme phenylalanine hydroxylase, with molecular oxygen (O_2) and tetrahydrobiopterin as cofactors. L-Tyrosine is converted into L-DOPA by the enzyme tyrosine hydroxylase, with tetrahydrobiopterin, O_2, and iron (Fe^{2+}) as cofactors. L-DOPA is converted into dopamine by the enzyme aromatic amino acid decarboxylase (AADC; Figure 1a, b), with pyridoxal phosphate as the cofactor. Later on, cytoplasmic dopamine within the neurons is transported into the secretory vesicles by vesicular monoamine transporter (VMAT 2). Presence of dopamine transporters (DAT) on the plasma membrane presynaptic neurons uptake of dopamine occurs back to the cytosol. Ion concentration gradient generated by the plasma membrane Na+/K+ ATPase facilitates the process of dopamine uptake. Further, cytosolic dopamine can be packed in the synaptic vesicles or metabolized. Metabolic action transformed the dopamine in to inactive metabolite. For these transformation different enzymes such as monoamine oxidase (MAO), catechol-O-methyl transferase (COMT), and aldehyde dehydrogenase (ALDH) are involved in the breakdown process (Eisenhofer *et al*., 2004). Both the isoforms of monoamine oxidase enzyme (type A MAO and type B MAO) effectively metabolize dopamine (You dim *et al*., 2006) into 3, 4-dihydroxyphenylacetic acid (DOPAC). In higher vertebrates, action of catechol-O-methyltransferase (COMT) degraded dopamine into 3 methyltyramine (3MT) and converted to homovanillic acid by MAO (Figure 1a, b)

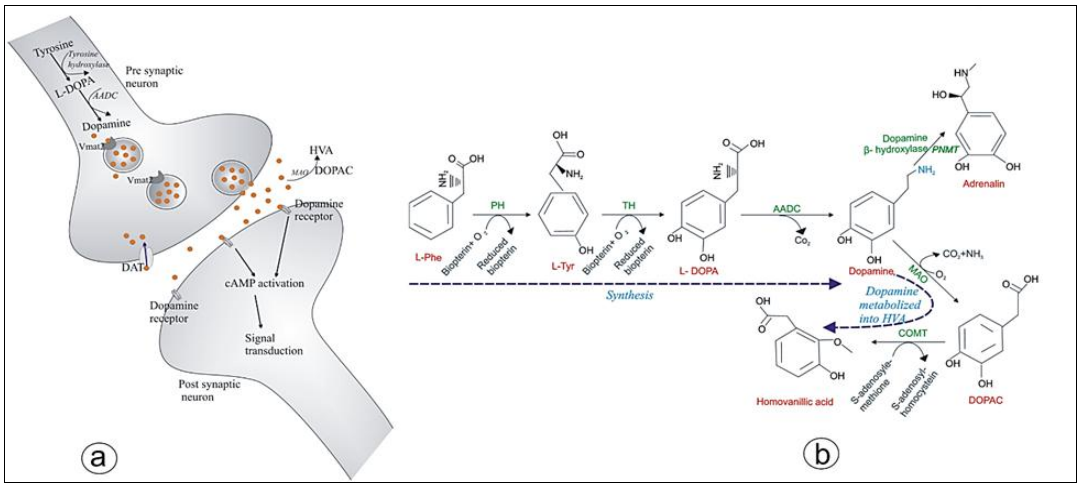

Fig 1: Schematic representation of the dopamine synthesis and metabolic pathway. L-DOPA, Dihydroxy phenylalanine; AADC, Aromatic amino acid decarboxylase; Vmat2, Vesicular monoamine transporter 2; DAT- Dopamine transporter; DOPAC, 3,4-dihydroxyphenylacetic acid; MAO, Monoamine oxidase; COMT, Catechol-O-methyl transferase; 3MT, 3 methyltyramine; HVA, Homovanillic acid; PH, Phenylalanine hydroxylase; PNMT, Phenylethanolamine N-methyl transferase; TH, Tyrosine hydroxylase

In addition to the above, dopamine itself is used as precursor in the synthesis of neurotransmitters noradrenaline and adrenaline. Dopamine is converted into noradrenaline by the enzyme dopamine β-hydroxylase, with O2 and L-ascorbic acid as cofactors. Noradrenaline is converted into adrenaline (Figure 1 b) by the enzyme phenylethanolamine N-methyltransferase with S-adenylyl-L-methionine as the cofactor ((Musacchio *et al*., 2013) [31]. It is reported that deficiency in any required amino acid or cofactor can impair the synthesis of dopamine (Musacchio *et al*., 2013) [31].

Recent studies have shown that dopamine rapid release was generally triggered by fast calcium sensors at other synapses. However, the neurobiology behind the fast dopamine release of calcium sensing is unknown. Furthermore, reports on rodents have mentioned that dopamine fast signals require a calcium sensor protein that is often used for ultrafast signaling: Synaptotagmin-1 (Banarjee *et al*., 2020) [2]. Release and synthesis processes of dopamine in the brain also disrupts due to external environmental factors and pharmacological agents. Recently it was noted that genes related to dopaminergic signaling were significantly down regulated in the BPA treatment group and decreased serum dopamine concentrations suggesting that BPA may disrupt dopaminergic processes in the goldfish brain (Wang *et al*., 2019). Dopamine release in the brain is crucial for voluntary movement and it is strictly Ca2+- and electrical activity-dependent (Catoni *et al*., 2019) [10].

Neuroanatomical distribution of dopamine

The Central nervous system of higher vertebrates contains a large amount of DA, and the diverse locations of DA neurons in different brain regions show how this substance may be involved in a variety of central activities (Liu and Kaeser 2019) [27]. For example, DA modifies the function of the hypothalamus and pituitary. Moreover, dopamine in the brain is involved in the control of executive functions, motor control, motivation, arousal, reward, sexual behavior, and lactation. Recently dopamine involved in the development of immature neurons in the adult rat Piriform Cortex (Coviello *et al*., 2020) [13].

However, recent scientific literature on fishes demonstrated that dopamine neurons on the disease models may predict the equivalent structures of mammalian brain dopaminergic neurons in teleost fish. Majority of the studies have employed TH as a marker for labeling dopaminergic neurons, whereas some studies have also used DBH to differentiate between DAergic and NEergic neurons in teleosts (figure 2, a). In zebrafish, TH-immunoreactive neurons occur throughout the brain (Yamamoto *et al*., 2011; Semenova *et al*., 2014) [58, 48]. DA expressed in the olfactory bulb and the ventral telencephalic area, whereas in the hypothalamus, DA neurons were extensively found in anterior and posterior parts of the parvocellular preoptic area, the suprachiasmatic nucleus, the periventricular pretectum, the ventral thalamus, the periventricular nucleus of the *posterior tuberculum* and the paraventricular organ, the posterior tuberal nucleus and in the caudal hypothalamus (Kaslin and Panula, 2001; Rink and Wullimann, 2001) [22, 42]. Distribution of DA in the goldfish (Kah *et al*., 1984, 1987) [20], trout (Linard *et al*., 1996) [26], and European eel (Vidal *et al*., 2004) [51] have shown that the DA neurons responsible for the inhibitory control of reproduction involves preoptic area and project directly to the PPD region of pituitary gland (Kah *et al*., 1984, 1987) [20]. Furthermore, the Fontaine *et al*. (2013) [18] using double-immunolabeling technique, observed a dense network of TH-ir fibers terminating near LH β-producing GtH cells in the zebrafish. Collectively, these studies in different fish groups apparently suggest a potential role for DAergic neurons of the NLT, the POA and the NPO regions in regulation of LH.

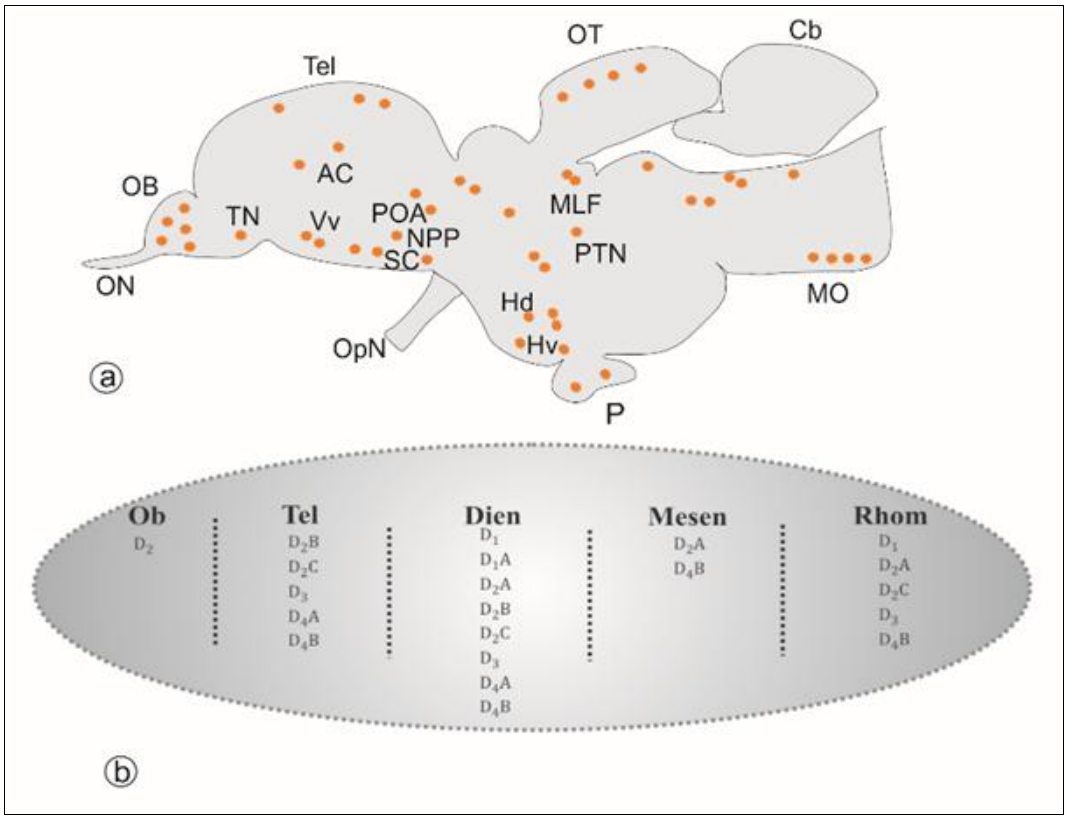

Fig 2: A diagrammatic representation of the fish brain shows the dopamine/Tyrosine hydroxylase localization in the different compartments of the brain (a). The schematic diagram (b) shows the presence of different receptor types in the fish brain regions. AC, Anterior commissure; AP,

Area postrema; Cb, Cerebellum; Hd Dorsal hypothalamus; Dien, Diencephalon; Hv, Ventral hypothalamus; LX, Vagal lobe; OB, Olfactory bulb; ON. Olfactory nerve; OpN, Optic nerve; OT, Optic tectum; Tel, Telencephalon; TN, nervus terminalis; MO, Medulla oblongata: Mesen, Mesencephalon; Rhombencephalon, MLF, nucleus of medial longitudinal fascicle; NPO, Nucleus preopticus; POA, preoptic area; P, Pituitary; PTN, *Posterior tuberculum*; PVO, Paraventricular organ; SC, suprachiasmatic nucleus; Vv, Area ventralis of telencephali pars ventralis (Distribution data composed from Sébert *et al*., 2008; Kumar *et al*., 2014; Yamamoto *et al*., 2011; Semenova *et al*., 2014; Singh *et al*., 2012; Bhat *et al*., 2017; Chabbi *et al*., 2015. Distribution of receptors taken from the Fountain *et al*., 2013; Bundschuh *et al*., 2012; Maximo and Hurculano, 2010) [46, 24, 58, 48, 50, 3, 11, 61, 8,].

Recent reports on the fishes also mentioning the distribution and involvement of Dopamine in the different physiological mechanism. Kumar *et al*. (2014) [24] studied the tyrosine hydroxylase in the olfactory system, forebrain and pituitary of the Indian major carp, *Cirrhinus cirrhosis.* In catfish Interaction between dopamine- and is otocin containing neurons in the preoptic area involve in the in the regulation of luteinising hormone cells (Singh *et al*., 2012) [50]. In addition to this Sex differences in the expression of gonadotropin-releasing hormone, and tyrosine hydroxylase family genes in the medaka brain was recently been reported (Kawabata *et al*., 2012) [23]. Moreover, an expression pattern of tyrosine hydroxylase was significantly higher in females compared with males, during early brain development (Mamata *et al*., 2014) [62]. In the viviparous fish, *Gambusia affinis* distribution pattern of tyrosine hydroxylase neurons in the olfactory bulb, telencephalon and mid brain were well studied and suggests the diverse roles of dopamine in various physiological functions (Bhat *et al*., 2017) [3]. Chabbi *et al*. (2015) [11] demonstrated the localization of TH in the POA and pituitary of the female cichlid fish, and suggested an additional pathway for the inhibitory effects of stress through dopaminergic neurons along the reproductive axis. In the Indian major carp, Saha *et al*. (2015) [45] examined the Interaction between dopamine and neuropeptide Y in the telencephalon of the Indian major carp, *Cirrhinus cirrhosis* and suggested the role of peptide in the central regulation of reproduction in teleosts.

Dopamine receptors in fish brain

It is well examined, that DA and its receptors is widely distributed in the vertebrate brain and is involved in reproduction, neuroendocrine responses, motor activity and several neurological disorders. In mammals, Dopamine controls various physiological functions by acting on its G protein–coupled D1, D2, D3, D4, and D5 receptors (Seeman, 2009) [47]. In fish, two types of G protein-coupled receptors, the D1 and D2 receptor families (figure 2 b), mediate the regulatory roles of dopamine neurotransmission, which controls a variety of brain activities (Popesku *et al*., 2011) [38]. Recently maximum nine DA receptor subtypes were reported in the fishes (Yamamoto *et al*., 2015) [57]. Four subtypes noted from the D1 family, D1, D5, D6, and D7 while the D2 family would enclose five subtypes, D2, D3, D4, D8, and D9. In zebrafish, *Danio rerio*, these nine DA receptors subtypes have been isolated (Yamamoto *et al*., 2015) [57], except for D7, D8 (D2b in Boehmler *et al*., 2004) [6], D3 and D9 (D4b in Boehmler *et al*., 2007) [5] encoded by a unique gene, the D1, D5, D6, D2 and D4 receptor subtypes are encoded by two paralogous genes. As per the evolutionary framework the occurrence of these DA receptors type was attributed due to teleost-specific genome duplication (Yamamoto *et al*., 2015) [57].

Recently Roche *et al*. (2020) [43] identified ten DA receptors belongs to D1 and D2 family mRNAs isolated from the brain of pikeperch at the pre-ovulatory period. Compared to peripheral organ, higher expression of the receptors in the pikeperch fish brain suggests the importance of DA in neurophysiological functions. Several genes encoding D2-receptors have been recognized in teleosts such as the zebrafish (Boehmler *et al*., 2004) [6], the European eel (Pasqualini *et al*., 2009) [33] and the goldfish *Carassius auratus* (Popesku *et al*., 2011) [38]. Above mentioned teleost-specific paralogs for some subtypes and even spliced variants within fish brains highlighted the complexity of DA receptors in the fishes. These receptors are differentially expressed in different brain areas and in the pituitary (Figure 2, b)**.** D1 family receptor complex regulates the decrease in serum LH levels and aromatase B transcript levels in the hypothalamus of the goldfish, *Carassius auratus* (Popesku *et al*., 2010; 2012) [40]. It is well understood that DA, acting through the D1 and D2 receptor, stimulates growth hormone release and inhibits luteinizing hormone (LH) release, respectively (Popesku *et al*., 2008) [39]. In zebra fish, DA has a direct and potent inhibitory action in the neuroendocrine control of reproduction through DA D2-Receptor subtype expressed on the LH cells (Fontane *et al*., 2013) [64]. Reports are also available on sex steroid alters dopamine receptors in the fish brain. E2 Treatment increased the pituitary mRNA levels of DA-D2 receptors with increased expression of GnRH receptor in tilapia (Levavi-Sivan *et al*., 2006) [25]. In *in vivo* experiments D1 receptor family, but not D2 family, is involved in the regulation of sex steroid production in pikeperch during the final oocyte meiotic maturation (Roche *et al*., 2018) [44]. Effect of Dopamine 2 receptor antagonist, haloperidol an active neuroendocrine element on reproductive behaviors was studied in fathead minnow ((Villeneuve *et al*., 2010) [52]. Moreover, in the slice superfusion, NPY immunoreactivity in EN neurons responded to DA D1-like receptor agonist treatment (Saha *et al*., 2015) [45]. Xing *et al*., 2015 [56] have demonstrated that D1receptor activation regulates the estrogen synthesis enzyme aromatase B, which may be regulates the neural regeneration, and neuroendocrine functions. In addition to this, Hamilton *et al*. (2017) [19] demonstrate that the dopamine D1-receptor agonist (SKF 38393) induces the formation of object recognition memories in coral reef fish. Recent studies accumulated the information of the dopamine receptors and their involvement in the different physiological activities in the fishes. Yet more research experimentations needed with the dopamine receptors activators (D1 and D2) to explore the role of these receptors to influence not only HPG but other physiological mechanisms in fishes.

Dopamine in fish reproduction

In fish, special tract hypothalamo-hypophyseal tract (HHT) involved to influence the neuroendocrine regulated reproductive activity. However, mechanism of reproductive control in non-mammalian vertebrates is not always the same as in mammalian models (Zohar *et al*., 2010) [60]. For example, in teleost fish, hypothalamic hormones that control pituitary functions are directly transported to the respective pituitary endocrine cells via neuronal fiber projections (Rao *et al*., 1993) [41]. For the first time in teleost, it was reported that

dopamine directly inhibits the hypothalamic GnRH1 neurons via activation of dopamine type-2-like receptor (D2R) in the cichlid fish (Bryant *et al*., 2016) [7]. DA system interacted with pituitary and regulate the reproduction through the HHT tract was well reported. Dopamine and isotocin-containing neurons in the preoptic area of the catfish, *Clarias batrachus*, were recently reported to regulate the luteinising hormone cells (Singh *et al*. (2016)) [49]. Further authors suggested that interaction between isotocine and dopamine NPPa neurons in POA is most probably of an inhibitory nature and controls the reproduction in teleosts. Hypophysiotropic DA neurons of the nucleus preopticus periventricularis (NPP), located in the anteroventral POA, have been shown to be sexually dimorphic in *C. batrachus*. (Saha *et al*., 2015) [45]. Furthermore, Fontaine *et al*. (2013) [18] observed a dense network of TH-ir fibers terminating near LH β-producing GtH cells in the zebrafish. Collectively, these studies in different fish groups apparently suggest a potential role for DAergic neurons of the NLT, the POA and the NPO regions in regulation of LH. Although as per above number of studies have shown to exert inhibitory effect of dopamine on LH secretion in a majority of teleosts (Dufour *et al*., 2010) [55], whereas no effect of DA on GtH was observed in the Atlantic croaker *Micropogonias undulatus* (Copeland and Thomas, 1989) [12].

Recent Accumulating evidences suggest role of DA on reproductive axis during stress. In stress condition it is reported that TH/DA secretory activity in specific regions of the fish hypothalamus. DA secreting neurons in the POA and the n PO regions were responded in the stress in the tilapia *O. mossambicus* (Chabbi and Ganesh, 2015) [11]. In fish exposed to aqua cultural stressors noticed densely labeled DA-ir cells in the POA and the NPO regions, concomitant with weak LH-expression and increased TH immunoreactivity fibres in the PPD. Further in mosquito fish, Bhat and Ganesh (2020) [4] has demonstrated the neuroanatomical relationship between DA and GnRH during stress condition in fish.

It is well documented that the brain is one of the specific target tissues for sex steroid hormones and the identification of its related receptors in the different regions of the central nervous system suggests a role for sex hormones in modulating neuroendocrine related brain functions (Dufour *et al*., 2010) [55]. Sex steroids have been shown to exert complex effects on the teleost hypothalamic compartments, with differential effects depending on the species, pharmacological parameters (dose, route of administration) and physiological status of the animals (Weltzien *et al*., 2006) [63]. Gonadal steroids also may function, in part, to upregulate neurosteroid production and collectively involved in the modulation of neural circuits (Diotel *et al*., 2010) [14]. Dopamine enhances the steroidogenic function by upregulating estrogen synthesis enzymes through its receptors (Xing *et al*., 2015) [56]. Fish gonadal stimulation by dopamine agonists and antagonists demonstrated the role of dopamine in the reproduction. Number of ovarian follicles (Stage V) in the female fish significantly increase in the tilapia following domperidone (DA receptor antagonist) in the tilapia (Chabbi and Ganesh, 2015) [11], similar reports were also noticed in the viviparous fish *G. affinis* with increase doses of domperidone (Bhat and Ganesh, 2020) [4]. In contrast to this, Pham and Arukwe, (2013) [35] findings suggest that DOM may not be needed for the induction of maturation and spawning of waigieu seaperch. Moreover, no effect of domperidone was noticed on oocyte maturation and spawning performances in the rabbit fish, *Siganus guttatus* (Pham and Le, 2016) [36]. Above reports conclude that the differences in the response of receptors might be due to fish species specific on the gonads. In support to this recently Roche *et al*. (2018) [44] have demonstrated that D1, but not D2, dopamine receptor regulates steroid levels during final stages of gametogenesis in pikeperch.

Conclusions and future directions

Recent studies explore the inhibitory role of dopamine containing hypothalamic neurons in the reproductive axis. Early studies suggested a hypothalamic site of dopaminergic GnRH1 whereas recently shown that selective activation of dopamine type-2 receptors involved to inhibits hypothalamic GnRH1 cells. To further understand the action of DA and its related receptors to induce HPG axis more research is needed on the action of receptors in a different fish species.

It has been shown that DA and Gnu RH interlinked in the stress and reproduction in fish. Stress inhibits follicular development and subsequent hatching success through the suppression of Gnu RH and that the inhibition appears to be mediated through dopamine in viviparous fish. Additional study required to discover the stress related neuronal network and its impact on reproductive axis in fish. It was demonstrated that dopaminergic system is one of the target places for kiss peptin, serotonin, isotocin and feeding related peptides at the level of NPP in the brain. The study of localization and the application of pharmacological substances to the brain will open up a new area of brain dopaminergic interaction and crosstalk network with other neuropeptides/neurotransmitters.

Although the inhibitory role of dopamine containing hypothalamic neurons, and DA and Gnu RH interlink in the teleosts brain under stressful conditions, differentiation and regulation of the dopaminergic preoptico-hypophysial neurons specifically in *D. rerio* and *O. latipes* fish model were recently explored. Dopamine as per their presence of multiple, conserved dopaminergic control sites within the hypothalamus may have more potential to uncover the functional features in the brain of fish. Focusing on the specific dopaminergic neurons within the hypothalamus will help to understand how they differentiate and establish connections and then organize into functional networks.

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