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Exploring cardiac plasticity in teleost: the role of humoral modulation

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ABSTRACT

The fish heart represents an established natural model for evaluating basic mechanisms of the coordinated physiological reactions which maintain cardiac steady-state. This is due to its relatively simple design, but also to its multilevel morpho-functional flexibility which allows adequate responses to a variety of intrinsic (body size and shape, swimming performance, etc.), and extrinsic (temperature, salinity, oxygen level, water chemistry, etc.) factors related to the animal life style. Nowadays, although many gaps are still present, a huge literature is available about the mechanisms that fine-tune fish cardiac performance, particularly in relation to the influence exerted by substances possessing cardio-modulatory properties. Based on these premises, this review will provide an overview of the existing current knowledge regarding the humoral control of cardiac performance in fish. The role of both classic (i.e. catecholamines, angiotensin II and natriuretic peptides), and emerging cardioactive substances (i.e. the chromogranin-A-derived peptides vasostatins, catestatin and serpinin) will be illustrated and discussed. Moreover, an example of cardiomodulation elicited by peptides (e.g., nesfatin-1) associated to the regulation of feeding and metabolism will be provided. The picture will hopefully emphasize the complex circuits that sustain fish cardiac performance, also highliting the power of the teleost heart as an experimental model to deciphering mechanisms that could be difficult to explore in more elaborated cardiac morpho-functional designs.

1. Introduction

The fish heart is characterized by an impressive cardiac morpho-functional heterogeneity which covers all levels of organization, from gross morphology to molecular biology (Olson, 1998; Tota et al., 2010). Heterogeneity is also observed within the same heart as a result of modular morphogenesis driven by distinct transcriptional regulatory programs (ref. in Tota and Garofalo, 2012; Imbrogno, 2013). Examples are provided by chamber formation, trabeculation pattern, localized pacemaker activity, and organization of the atrio-ventricular region and of the outflow tract (Icardo, 2006; Icardo and Colvee, 2011). As in other vertebrates, in fish the heart is able to adjust its hemodynamics in response to both intrinsic and extrinsic signaling pathways, thus supporting the varying physiological requirements of the animal (see for example Gamperl and Farrell, 2004; Amelio et al., 2013). This is exemplified by the beat-to-beat modulation of contractility in response to changes in volume and pressure loads (i.e., the Frank-Starling response) and by the adaptive cardiac morpho-functional rearrangement. Plasticity is driven by an increasing number of neuroendocrine factors which exert a multilevel regulation, controlling cell, tissue, and organ form and function. It also involves the secretory ability of myocardial and endocardial endothelial (EE) cells that, under normal and stressfull conditions, release autocrine regulators (Tota et al., 2010). In fish, the autocrine-paracrine-endocrine regulation of the heart appears very relevant (Tota et al., 2010; Imbrogno et al., 2011; Imbrogno and Cerra, 2017). A proliferation of data on the functional importance of cardioactive hormones, their receptors, and the downstream signalling pathways has recently accumulated particularly in teleosts. This added new information and points of discussion, also stimulating novel interest in this field of research. In this review, by using teleosts as a frame of reference, we will illustrate how the morpho-functional heterogeneity of the fish heart may be humorally integrated/coordinated to support the uniformity of the whole-organ performance. The purpose is also to highlight the power of the teleost heart as an important conceptual tool to explore the humoral-mediated signal-transduction pathways which allow the heart to detect, interpret and respond to beat-to-beat, short-term and long-term challenges. Firstly, for the unfamiliar reader, a brief outline of the basic morpho-functionl design of the teleost heart will be provided.

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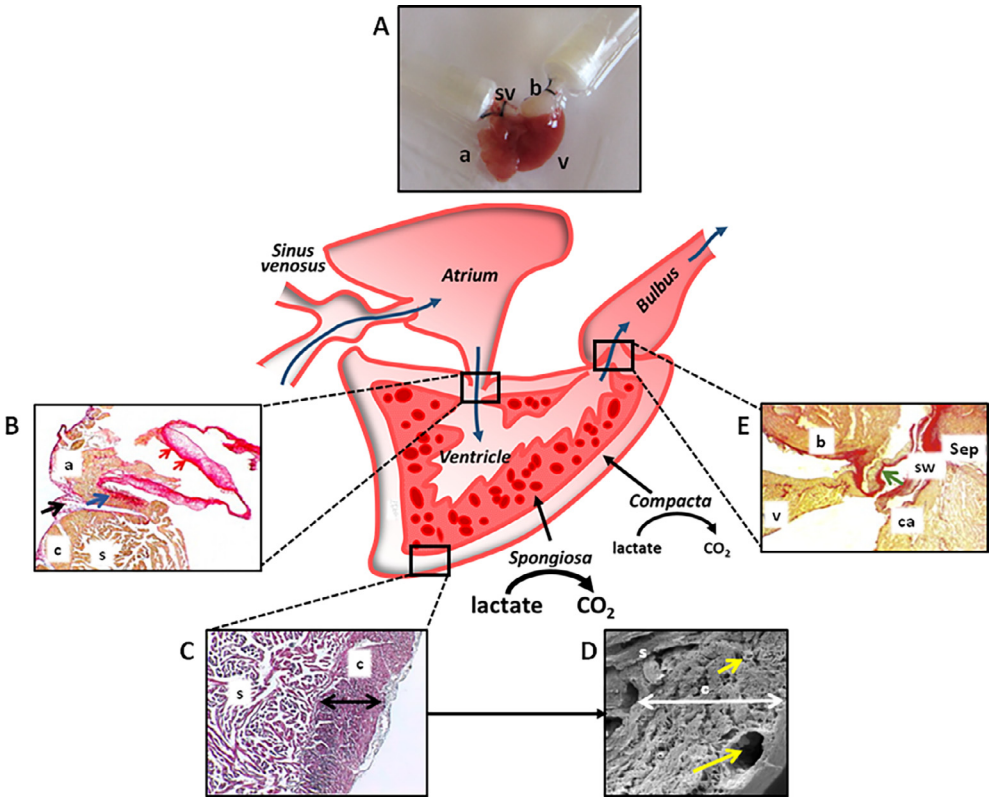

Fig. 1. The goldfish (*C. auratus*) heart. (A) Lateral view. a, *atrium*; b, *bulbus*; v, ventricle; sv, *sinus venosus*. (B) Longitudinal section of the atrio-ventricular region (Sirius red staining for collagen identification). The connective ring (black arrow) surrounding the vascularized muscular tissue (blue arrow) is evident. Red arrows indicate the thick fibrosa of the atrio-ventricular valves (Garofalo et al., 2012). (C) Hematoxilin-eosin stained ventricular section showing *compacta* (c) and *spongiosa* (s) (D. Amelio unpublished data, for gentle permission). The black arrow indicates *compacta* thickness. (D) SEM micrograph illustrating details of *compacta* (c) and *spongiosa* (s); vessels in the *compacta* are indicated (yellow arrows) (Garofalo et al., 2012); white arrow: *compacta* thickness. (E) Sirius red staining of the *conus arteriosus* showing the high collagen amount (green arrow) in the thick fibrosa (ventricular layer of the conus valve leaflets) (Garofalo et al., 2012). The great ability of the spongy layer to oxidize lactate to CO_2 is indicated (modified from Gattuso et al., 2018). b = *bulbus*; a = *atrium*; v = ventricle; c = *compacta*; s = *spongiosa*; ca = *conus arteriosus*; sw = *sinus wall*; Sep = *subepicardium*.

2. The teleost heart: morpho-functional traits

2.1. Morphological traits

The structural organization of the fish heart has represented a fascinating field of research, whose outcomes are excellently reviewed in many papers (Santer, 1985; Farrell and Jones, 1992; Tota and Gattuso, 1996).

The teleost heart is formed by four chambers in series, i.e. the *sinus venosus*, the *atrium*, the ventricle and the outflow tract (*bulbus cordis*), and by other two distinct structures: the atrio-ventricular (AV) region, that supports the AV valves, and the conus arteriosus that, interposed between the ventricle and the bulbus arteriosus, supports the conus valves (Icardo and Colvee, 2011; Icardo, 2012; Schib et al., 2002) (Fig. 1). The blood flows in sequence from the *sinus venosus* to the *atrium*, the ventricle and the *bulbus cordis*; then, it is pumped to the gills to be oxygenated and distributed to the body.

The *sinus venosus* rapresents the most caudal portion of the heart, separated from the atrium by the sinus valve. Its wall is generally thin and formed by muscle bundles embedded in connective tissue, whose amounts varies between species (Icardo, 2017). From a functional point of view, the contraction of the *sinus venosus* contributes to a *vis-a-tergo* atrial filling. However, this can not be considered a general feature because of the sparse muscular content of the *sinus* wall in many specie, and the paucity of venous valves to prevent backflow (see Icardo, 2017 for references).

Located in a dorsal position relative to the ventricle, the atrial chamber is formed by a rim of myocardium enveloping a complex system of thin trabeculae. As observed in several teleost species (Icardo, 2012; Santer, 1985) atrial trabeculae, which consist of a myocardial core surrounded by endocardium, generally radiate from (or converging to) the AV orifice.

Two major types of ventricular organization can be encountered in fish: trabeculated and mixed (Tota, 1983). The trabeculated ventricle is made up of a crisscrossed array of myocardial bundles (*trabeculae*) that give the ventricular wall a spongy appearance (i.e. *spongiosa*). The *spongiosa* is avascular and is supplied by the intracavitary venous blood, which perfuses the inter-trabecular spaces (*lacunae*). The numerous *trabeculae* of the *spongiosa* generate an extensive network of lacunae that are lined by a thin layer of EE. This results in a very large EE surface that is of remarkable functional importance since it mediates the communication between blood-born stimuli and the subjacent myocardium (Imbrogno et al., 2001; Garofalo et al., 2009; Imbrogno et al., 2018). In many teleosts, the *spongiosa* is covered by a subepicardial outer layer of densely arranged myocardial bundles, the *compacta*, perfused by an arterial supply, thus forming a 'mixed type' ventricle (Tota, 1983; Tota et al., 1983; Icardo et al., 2005) (Fig. 1). Desmosome-like and fascia-adherens-like structures have been observed between the *compacta* and the *spongiosa* of various teleost hearts (Pieperhoff et al., 2009). Functioning as anchorage patterns, these structures provide a morpho-functional linkage between the two muscular layers, thus contributing to prevent ventricular dyssynergy (Pieperhoff et al., 2009). From a functional point of view, the *spongiosa* and the *compacta* show peculiar regional traits that contribute to organ homogeneity. An example is represented by the enzymatic activities that in the *spongiosa*, directly exposed to the circulating blood and the consequent higher oxygen availability than the *compacta*, are better suited for aerobic metabolism and waste (e.g. lactate) removal (ref. in Gattuso et al., 2018) (Fig. 1).

The outflow tract is formed by a proximal *conus* and a distal *bulbus arteriosus*. The *conus arteriosus* is formed by compact myocardium, which is generally vascularized and supports the conus valves (Schib et al., 2002). This region is easily detectable in fully trabeculated ventricles, but it is more difficult to be recognised in those possessing a compact layer. The *bulbus arteriosus* is organized into outer, middle, and inner layers. As described by Icardo and colleagues in the eel (Icardo et al., 2000), the inner bulbar wall shows an irregular surface due to the presence of branching ridges, covered by flattened EE cells. These cells contain membrane-bound vacuoles, identified as moderately dense bodies, and suggested to be the storage of different molecules with

different functional roles (Icardo et al., 2000). Accordingly, the teleost bulbus, in addition to its physical properties as a pressure chamber, may represent a secretory region able to respond to physical and chemical stimuli with the release of paracrine/endocrine factors that may contribute to cardiovascular modulation, also acting on the subjacent smooth muscle (Icardo et al., 2000). In many teleosts, the middle layer of the bulbus is formed of smooth muscle, arranged into irregular cell layers, embedded within a filamentous matrix, and differently oriented (see Icardo et al., 2000 and references therein). The stretching of this meshwork suggests an active role of smooth muscle in wall dynamics. In this region, large areas of the extracellular space are occupied by elastin-like materials, whose amount decreases toward the external layer. This provides the bulbus of important elastic properties that contribute to properly control blood flow to the gills (Icardo et al., 2000). On the contrary, the collagen, although present across the entire wall thickness, increases from the inner toward the outer bulbus surface. Conceivably, such gradient of collagen matrix may increase wall strength, maintaining bulbus dilation within safe physiological changes. The outer layer (the sub-epicardial tissue) is formed by a loose connective tissue, rich in collagen and that contains fibroblasts, vessels and unmyelinated nerves. Micropinocytosis vescicles populate epicardial cells, suggesting an active solute exchange with the pericardial cavity (Icardo et al., 2000).

2.2. Functional traits

The above described myocardial arrangement represents the prerequisite for the peculiar pumping performance of the teleost heart. This is remarked by the high extensibility of the trabeculated myocardium, and the ability to maintain an increased myofilament Ca^{2+} sensitivity over a wide range of sarcomere lengths, both considered basic traits of the high sensitivity of the fish heart to preload challenges (Di Maio and Block, 2008; Shiels and White, 2008).

As in the other groups of vertebrates, in fish the regulation of cardiac output (CO), i.e. the product of heart rate (HR) and stroke volume (SV), is obtained through both intrinsic and extrinsic (neurohumoral) mechanisms. The intrinsic control, exemplified by the length-dependent response to changing preload (i.e., the Frank-Starling mechanism) is commonly recognized as a major regulator of fish cardiac performance (Olson, 1998). It is well acknowledged that in teleost [e.g., icefish (Tota et al., 1991), salmon (Gattuso et al., 2002), gilthead seabream (Icardo et al., 2005), eel (Imbrogno et al., 2001; Angelone et al., 2012a), goldfish (Garofalo et al., 2012; Imbrogno et al., 2014)], this represents a major mechanism of regulation of cardiac performance. In parallel, the fish heart is regulated by the autonomic nervous system. Innervation occurs *via* a 'vagosympathetic' trunk (Laurent et al., 1983; Newton et al., 2014), whose importance is species-specific. In many cases, a parallel presence of catecholamine (CA)-containing chromaffin cells into hemodynamically important districts provides an additional regional adrenergic release, which contributes to cardiovascular modulation (for references and details, see Tota et al. 2010).

3. Catecholamines in the basal control and stress response

The teleost heart is exposed to an adrenergic modulation elicited by both adrenergic terminals and chromaffin cell-derived CA.

Intense research carried out since middle 1990ies has evaluated the relative involvement of humoral and neural CA in the modulation of the heart performance and of the stress response. Unfortunately, the discrepancies in the extent of the adrenergic neuronal innervation amongst species, the inter-specific variability in the plasma levels of CA, as well as the organizational level under study (i.e. *in vivo* cardiovascular system versus isolated and denervated working heart) prevented to reach a general conclusion, inclusive of all teleost species.

It is commonly assumed that in teleosts basal plasma CA levels are low, whereas the nervous activity plays a major role (Smith, 1978; Holmgren and Nilsson, 1982; Smith et al., 1985; Axelsson, 1988; Randall and Perry, 1992). In response to various physical and environmental stimuli (exhaustive exercise, hypoxia, hypercapnia, etc.), chromaffin cells, such as those located close to the head kidney, into the walls of the posterior cardinal vein, release CA into the circulation (Nandi, 1961). These circulating CA, plus those released by nerve terminals and cardiac chromaffin cells (Nilsson and Holmgren, 1992; Farrell and Jones, 1992), exert cardiac, vascular and respiratory responses, thus contributing to alleviate stress-induced detrimental effects (Farrell et al., 1986). However, stress-tolerant fish, such as the members of the genus *Anguilla*, do not show increased plasma CA in response to stressful stimuli (Imbrogno, 2013).

The heart response to CA stimulation is mediated by α- and β-adrenoreceptors (ARs) and their subtypes, identified in fish, as well as in other vertebrates (Ask, 1983). A basal adrenergic excitatory tone, which prevails over the cholinergic tone, has been described by Pennec and Le Bras (1984) in the eel *Anguilla anguilla*, although more recent studies reported considerably higher cholinergic than adrenergic tones in various species (for references, see Sandblom and Axelsson, 2011). Adrenergic tone is mediated by α- and β-ARs associated with both the pacemaker and the working myocardium (Axelsson et al., 1987; Gamperl et al., 1994). Adrenergic stimulation has been reported to increase HR (Graham and Farrell, 1989) and slightly improve the Frank–Starling response (Farrell et al., 1986).

Several studies pointed out the influence of temperature on the cardiac response to ARs activation in teleost, making the picture even more complex. For example, Peyraud-Waitzenegger et al. (1980) correlated the function of cardiac ARs to thermal seasonal changes. More recently, it has been reported that chronic cooling increases β_2-ARs expression in the myocardiocytes of rainbow trout (*Oncorhynchus mykiss*) (Keen et al., 1993), and chinook salmon (*Oncorhynchus tshawytscha*) (Gamperl et al., 1998), while acute cooling increases the efficacy of adrenergic-dependent stimulation of the calcium current in rainbow trout myocytes (Shiels et al., 2003). In the bluefin tuna (*Thunnus orientalis*), adrenaline resulted more effective in acute warming, with respect to acute cooling (Shiels et al., 2015).

Early work on cardiac myocytes from the rainbow trout (*O. mykiss*) suggested that, in contrast to the three β-AR subtypes reported in the mammalian myocardium, only a β_2-AR orthologue is expressed in fish (Gamperl et al., 1994). However, more recent studies revealed that, as in mammals, also in the teleost heart the adrenergic control occurs through a β_3-AR type (Imbrogno et al., 2006; Imbrogno et al., 2015a). In 2003, Nickerson and coworkers detected in *O. mykiss* the presence of two previously unreported β-ARs (adrb3a: NP_001118100; adrb3b: NP_00117924). These two β-ARs were found to be homologous to the mammalian β_3-AR and highly expressed in both gills and heart. Subsequently, sequences similar to β_3-ARs were identified in various teleost species, including zebrafish (adrb3a: BAH84778, and adrb3b: NP_001128606), black bullhead (adrb3b: ABH10580), stickleback (ENSGACP00000014582) and fugu (ENSTRUP00000020 757). Despite these encouraging evidences, very few studies documented in teleost the role of the β_3-AR in the control of the cardiac function. In the freshwater eel *A. anguilla*, Imbrogno and coworkers showed that the activation of β_3-ARs elicits a dose dependent negative inotropism (Imbrogno et al., 2006). This effect occurs through a pertussis toxin (PTx)-sensitive G_i protein mechanism, and requires the Nitric Oxide (NO)-cGMP-protein kinase G (PKG) pathway (Fig. 2). Moreover, in the eel, isoproterenol (ISO) stimulation, in addition to its classic cardiostimulation, induces a reduction of contractility possibly mediated by β_3-AR (Imbrogno et al., 2006) (Fig. 2). This suggests a cardio-inhibitory protection versus systemic and/or intracardiac cascades of excitatory stimuli targeting the heart, including β_2-AR-mediated effects. In the common carp, β_3-AR stimulation by BRL_{37344} was found to be associated with a significant reduction of SV (Petersen et al., 2015). Opposite to this cardio-inhibition, in the channel catfish, BRL_{37344} administration is accompanied by a stimulation of both contractility and

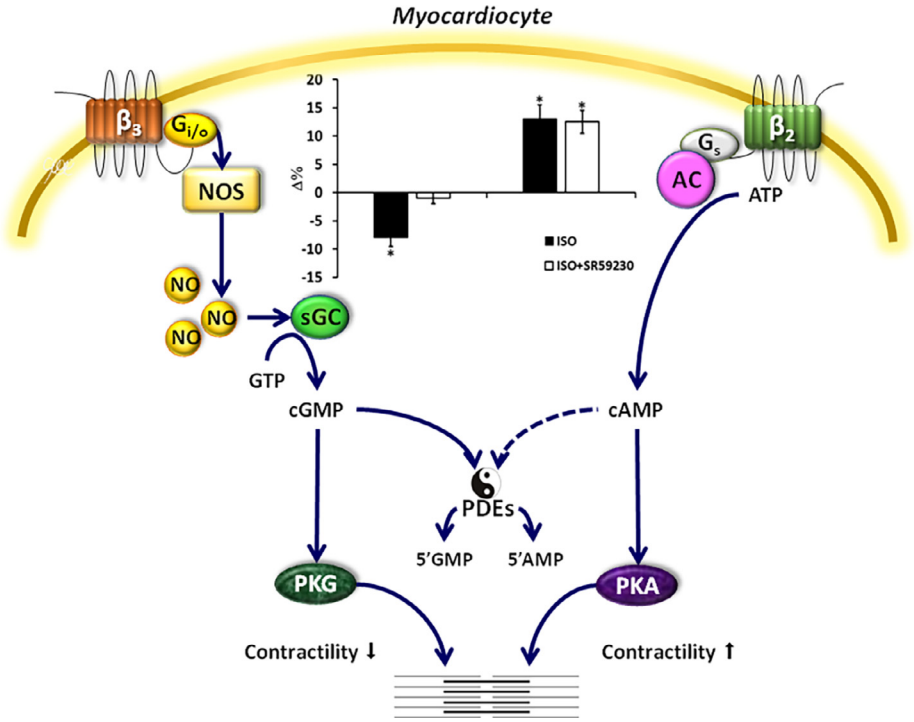

Fig. 2. β-AR-dependent modulation of fish cardiac contractility. The scheme shows the putative interplay between β_3-AR- and β_2-AR-mediated pathways, and their modulatory action on contractility. Ying–yang represents PDEs isoenzymes-mediated control of cGMP and cAMP levels. The bar graph shows the effects of isoproterenol (ISO; 100 nmol L^{-1}) on the stroke volume (SV) of the isolated and perfused eel heart. Note that ISO reduced contractility in about 30% of cardiac preparations (left black bar), while increased it in about 70% of preparations (right black bar). ISO-dependent cardio-inhibition is abolished by the β_3-AR antagonist SR_{59230} (10 nmol L^{-1}) (left white bar), that unaffected ISO-induced cardio-stimulation (right white bar). For ref. and details see the text.

HR (Petersen et al., 2015). These differences, that suggest a species-specific pattern of β_3-ARs-dependent cardiac control in teleost, possibly reflect the involvement of either Gs- or G_i-mediated mechanisms (Skeberdis et al., 2008; Angelone et al., 2008a). In mammals, it has been proposed that the stimulation of β_3-ARs, through a Gs protein-dependent enhancement in cAMP, is associated with a HR increase. Contrarily, an elevation of intracellular cGMP after nitric oxide synthase (NOS) activation through Gi protein is related to a reduced contractility (for references, see Imbrogno et al., 2015a,b).

Also β_3-ARs-dependent cardiac effects are modulated by temperature. In 23 °C acclimated common carp, stimulation of β_3-ARs caused a significant reduction of SV. However, an opposite effect was observed in the channel catfish acclimated to the same temperature (Petersen et al., 2015).

A remarkable, and often neglected, trait of the responsiveness of the fish heart to adrenergic stimulation is the low vulnerability to CA-dependent cardiotoxicity. This is the case of trout and tuna that show a low susceptibility to ISO-induced myocardial necrosis. In fact, in these teleosts, the few lesions develop slowly and are mainly localized in the deep avascular spongy myocardial core (Poupa and Ostádal, 1969). Thus, these teleosts differ from homeotherms in which the hyperadrenergic stimulation in the so-called "sympathetic storm" is responsible for huge damages to the myocardium (Samuels, 2007). This highlights the power of the teleost heart as an experimental model, for translational and applicative studies aimed to increase the knowledge on the mechanisms that protect the heart against adrenergic stress, and that are not fully operative in the very susceptible mammalian myocardium.

4. Angiotensin II in the short- and long-term modulation

Teleost fish possess a functional Renin-Angiotensin System (RAS) analogous to that found in mammals (Kobayashi and Takei, 1996). The principal bioactive RAS component angiotensin II (AngII) was identified and sequenced in various teleost species, including the chum salmon *Oncorhynchus keta* (Takemoto et al., 1983), the Japanese goosefish *Lophius litulon* (Hayashi et al., 1978), and the American eel *Anguilla rostrata* (Khosla et al., 1985). Different angiotensin peptides are present in teleost, pointing to a relevant role of the RAS in fish. For example, [Asn^1,Val^5]AngII and [Asp^1,Val^5]AngII circulate in the blood of trout and eel (Conlon et al., 1996; Wong and Takei, 2012). In trout, angiotensinogen cleavage gives rise to [Asn^1]-AngII which, in the plasma, is converted to [Asp^1]-AngII by asparaginase (Conlon et al., 1996). Differently, in the eel plasma, asparaginase activity is low and the conversion occurs in liver and kidney, with angiotensinogen, not AngII, as substrate (Wong and Takei, 2012).

As in mammals, the teleost heart is characterized by an intracardiac RAS. This is based on several evidences. Cardiac AngII binding sites are present in teleosts [e.g. trout (Cobb and Brown, 1992) and eel (Imbrogno et al., 2013)]; ACE activity has been observed in the ventricle of teleost species, including *Heteropneustes fossilis, Clarias batrachus, Channa gachua, Anabas testudineus, Notopterus chitala* and *Monopterus cuchia* (Olson et al., 1997); immunoreactive AngII-like material has been described in the heart of the Antarctic teleost *Champsocephalus gunnari* (Masini et al., 1997).

Ang II cardiac effects are mediated by plasma membrane AT_1 and AT_2 receptors (de Gasparo, 2002; Cerra et al., 2001). In mammals, AT_1 mediates most of the AngII-induced effects on cardiac performance (i.e. chronotropism and inotropism) and rate of protein synthesis (see for ref. Imbrogno et al., 2003). In contrast, cardiac AT_2 receptor antagonizes AT_1 growth promoting effects *via* activation of a number of phosphatases. This receptor also activates the NO-cGMP signaling, either directly, or indirectly, through enhanced bradykinin or endothelial NOS (eNOS) expression (Dostal, 2000).

AngII receptors have been cloned in several fish (Marsigliante et al., 1996; Tran van Chuoi et al., 1998). For example, in the European eel (*A. anguilla*), an angiotensin receptor (cDNA sequence in the GenBank; accession number AJ05132) (Tran van Chuoi et al., 1998), 60% homologus with the mammalian AT_1 receptor (Russell et al., 2001), has been reported. Moreover, in the Japanese eel (*Anguilla japonica)*, molecular phylogenetic and synteny analysis showed a receptor type which shares the origin with the mammalian AT_2 receptor (Wong and Takei, 2013).

4.1. Short-term effects

The teleost heart is directly and indirectly influenced by AngII [e.g., eel (Bernier et al., 1999); trout (Oudit and Butler, 1995)]. Indirect effects are mediated either by CA or by a modulation of the adrenergic tone (Oudit and Butler, 1995; Bernier and Perry, 1999; Reid, 1992). For example, in the trout (*O. mykiss)*, the exposure to AngII induces an increase of CO and SV; a result inverted by the treatment with α-adrenergic inhibitors (Bernier and Perry, 1999). Moreover, intracerebroventricular injection of AngII induced a pronounced tachycardia. This effect has been attributed to a removal of the vagal tone, and associated to an AT_1-like receptor activation (Le Mével et al., 2008). In contrast, AngII administered to the isolated and *in vitro* perfused working eel (*A. anguilla*) heart elicited a direct cardioinhibition abrogated by CV_{11974}, an AT_1 receptor blocker (Imbrogno et al., 2003). Reasons for the different responses to AngII stimulation among teleosts are to date unclear. Apart from species-specific-related differences, a role of the organization level under study (i.e., intact cardiovascular system *vs in situ* heart *vs* isolated and denervated working cardiac preparation) may be hypothesized. For example, the AngII-mediated cardio-suppressive effect observed in *in vitro* working heart preparations of the eel may function as a local mechanism of cardio-inhibitory protection able to balance/oppose systemic cascades of convergent excitatory stimuli. *In vivo*, this effect could be overridden by the synergism with other cardiovascular excitatory stimuli (Imbrogno et al., 2003). Accordingly, in mammals, β-AR and AngII receptors, both activated under stress and emergency conditions, recruit different effectors to produce common responses, as in the case of the hypertrophic remodeling of the heart (Hazon et al., 1995; Gul et al., 2016).

4.2. Long-term effects

In mammals, particularly under pathologic conditions, AngII activates growth-promoting and/or growth-inhibiting factors, and/or angiogenic molecules to induce cardiac growth and remodelling (Huckle and Earp, 1994; Li et al., 1999; Chintalgattu et al., 2003; Rademaker et al., 2004). AngII-dependent long-term effects have been recently observed also in the teleost heart. Imbrogno and co-workers observed that in the eel (*A. anguilla)*, chronic administration of AngII enhances cardiac hemodynamic performance in response to afterload increases; this effect is paralleled by structural modifications of the heart ventricle and by an incremented expression of proteins involved in the cell growth (Imbrogno et al., 2013; Filice et al., 2017). Notable, the application of a selective AT_2 antagonist (CGP_{42112}), which cross-reacts with fish cardiac AngII receptors (Cerra et al., 2001; Imbrogno et al., 2013), revealed the involvement of this receptor subtype in the above-mentioned effects. Therefore, while in mammals AT_2 receptors generally offset or oppose AT_1-induced effects, and mediate anti-growth and apoptotic actions (Gallinat et al., 2000), in teleost they appear associated to growth-promoting responses (Imbrogno et al., 2013; Filice et al., 2017). Interestingly, AngII-treated eel hearts show an increased expression of a NOS recognised by mammalian anti eNOS-like isoform (Imbrogno et al., 2013). Since in mammals, a reduced eNOS-derived NO generation is responsible for Reactive Oxygen Species (ROS) formation (Wenzel et al., 2007), it is possible that in teleost the AngII-dependent increase of NO bioavailability contributes to cardio-protective programs (Imbrogno et al., 2013). Currently, the significance of the AngII-induced growth-promoting action in the teleost heart remains unknown. However, on the basis of these data, important differences may be expected between fish and mammals. In fact, while the long-term effects induced by neuro-humoral factors, including AngII, potentially contribute to the heart failure progression in mammals (Mehta and Griendling, 2007), they can be regarded as fundamental components of the cardio-protective program of the stress response in fish (Tota et al., 2010).

5. Natriuretic peptides as cardioprotective factors

Natriuretic Peptides (NPs) are a group of hormones consisting of at least five members, i.e. atrial NP (ANP), brain NP (BNP), ventricular NP (VNP), C-type NP (CNP), and *Dendroaspis* NP (DNP) (ref. in Tota et al., 2010). Released in response to cardiac stretch induced by hypervolemia, and characterized by potent diuretic, natriuretic and vasorelaxant properties, NPs are recognized as a major cardiovascular hormonal system in vertebrates. In mammals, NPs coordinate both direct chronotropic, inotropic and vasorelaxant responses, and indirect actions that reduce cardiac hemodynamic loads, thus exerting cardioprotective and osmoregulatory functions (Ruskoaho, 1992).

The teleost heart is a major site for NPs production, and this is a very old evolutionary acquisition. A hallmark of the morpho-functional heterogeneity of the teleost heart is represented by the different expression of NPs in various cardiac regions. For example, ANP is almost exclusively expressed in *atria*, BNP equally in *atria* and ventricles and VNP three-fold more in ventricles than in *atria* (Takei et al., 2018). In the eel, VNP is released from the ventricle in a constitutive pathway, while ANP is secreted from the *atrium* in a regulatory pathway (Takei et al., 2018). In the Atlantic salmon (*Salmo salar*), a peptide structurally and functionally similar to the mammalian ANP, namely salmon Cardiac Peptide (sCP), is present both in the *atrium* and ventricle (Tervonen et al., 1998; Arjamaa et al., 2000; Vierimaa et al., 2006). Also VNP is present in the *atrium* and ventricle of salmonids, as well as in the sturgeon (Takei et al., 2018; Takei, 2000; Inoue et al., 2005). sCP and VNP have been reported in pacemaker ganglionic cells and in cardiomyocytes of *S. salar*, suggesting a neuromodulatory and/or neurotransmitter role for both peptides (Yousaf et al., 2012). Regardless its major role as an endothelial hormone, in fish, CNP represents also a cardiac product, as shown in eel and trout (Loretz and Pollina, 2000; Inoue et al., 2003).

Four types of NP receptors (NPRs), named NPR-A, B, C and D, are present in vertebrates (ref. in Takei et al., 2011). In teleosts, like NPs, also NPRs are differently expressed in the cardiac regions. Major NP binding sites are located in the *atrium*, the ventricle and the outflow tract (*bulbus arteriosus*) (Cerra et al., 1992; Cerra et al., 1996). In the eel (*A. anguilla*), NPRA-type receptors locate in the ventricular EE, while NPRC-like receptors are present in the atrial and ventricular myocardium (Cerra et al., 1996). A receptor with high affinity for CNP, presumably NPRB, is also present in endothelial and epicardial layers of the *bulbus arteriosus* of the eel, in which a CNP-dependent modulation of bulbar hemodynamics (e.g. the Windkessel function) has been proposed (Cerra et al., 1996).

In teleost, NPs exert a crucial regulatory role at the interface between osmotic and cardiovascular homeostasis. To provide some examples, in the trout (*O. mykiss*), injection of isotonic saline induces an increase in blood volume and ANP secretion (Cousins and Farrell, 1996), and injection of exogenous ANP induces a potent diuresis and natriuresis (Duff and Olson, 1986). On the other hand, in the eel (*A. japonica*), although volemic challenges induce NPs release, a major stimulus for ANP secretion is the seawater-dependent high plasma osmolality, rather than the enhanced blood volume (Kaiya and Takei, 1996).

In parallel with the NPs-dependent osmoregulatory function, both direct and indirect evidences support the role of NPs as major cardioprotective factors (Olson et al., 1997). An acute stimulus for cardiac NPs release is the stretch induced by hypervolemia (Ruskoaho, 1992). Once released, NPs relax both arterial and venous vessels. The consequent increased compliance and decreased vascular tone prevent the excessive hemodynamic loads (Farrell and Olson, 2000), thus providing an effective control system for regulating mean circulatory filling pressure and therefore venous-return (Olson et al., 1997). This mechanism, which is additional and/or alternative to the Frank-Starling response, significantly contributes to the fish heart performance. Interestingly, in freshwater fish (e.g. trout), which experiences only

volume but not salt load, NPs are constitutively released (Olson and Duff, 1992). This suggests that fish NPs are better designed as volume than salt regulators (Johnson and Olson, 2008; Johnson and Olson 2009a), and represent a fundamental system to protect the heart from excessive load (Johnson and Olson, 2009b).

6. The chromogranin A-derived peptides vasostatins, catestatin and serpinin as cardiac stabilizers

Chromogranin A (CgA) is a 48 kDa glycoprotein belonging to the chromogranin/secretogranin family. It was identified almost five decades ago in secretory granules of adrenal chromaffin cells in which it is co-stored with CA and co-released with them following cholinergic stimulation (Helle et al., 2007; Winkler and Fischer-Colbrie, 1992). Soon after the first sequencing of bovine CgA, it has been extensively studied as to its expression, structure and function. Many studies revealed its ubiquitous distribution throughout the animal world, from invertebrates to mammals, remarking a notable phylogenetic conservation (Bartolomucci et al., 2011; Montero-Hadjadje et al. 2008; Tota et al., 2007; Helle et al., 2007).

In the heart, CgA has been identified in the cardiac conduction system and in the atrial myoendocrine granules of rodents (Steiner et al., 1990; Weiergraber et al., 2000), and in the ventricular myocardium of humans (Pieroni et al., 2007). Both in humans and rodents, it was found to be co-stored and co-secreted with CA (Steiner et al., 1990; Pieroni et al., 2007; Biswas et al., 2010). In non-mammalian vertebrates, CgA expression was detected in the secretory granules of frog atrial myocytes (Krylova, 2007).

Cell-, tissue- and species-specific proteolytic processing of CgA generates a number of regulatory fragments (ref. in Helle et al., 2007). Among others, these include vasostatin 1 (VS-1), vasostatin 2 (VS-2) (Aardal et al., 1993), catestatin (CST) (Mahata et al., 2010; Mahata et al., 1997), and the recently identified serpinin peptides (i.e., Serp and pGlu-Serp) (Koshimizu et al., 2011). For extensive review see (Tota et al., 2014).

CgA and the fragments it generates are under intensive investigations for their role as cardiovascular stabilizers (see for example Tota et al., 2014; Tota et al., 2004; Angelone et al., 2012b; Angelone et al., 2008b; Mazza et al., 2010, 2015b; Mahata et al., 2018). In teleost, the CgA-derived fragments VSs, CST, and the pGlu-Serp peptide, elicit direct cardio-inhibitory effects (Tota et al., 2004; Imbrogno et al., 2004; Imbrogno et al., 2010; Mazza et al., 2007; Imbrogno et al., 2017) (Table 1; Fig. 3). In particular, on the isolated *ex vivo* perfused working heart of the eel (*A. anguilla),* VSs and CST peptides induce a dose-dependent reduction of SV and Stroke Work (SW) (Imbrogno et al., 2004; Imbrogno et al., 2010). They also counteract the effects of β-adrenergic (ISO) stimulation (Tota et al., 2004) (Table 1), which is indicative of a cardioprotection in the presence of excitatory stimuli. A reduction of contractility in response to pGlu-Serp stimulation has been very recently observed in the eel (*A. anguilla*) and the goldfish (*Carassius auratus*) (Imbrogno et al., 2017).

Interestingly, the analysis of the cardiac signal transduction mechanisms evoked by the three peptides in teleost, shows aspects of uniformity and diversity with respect to the other group of poikiloterms

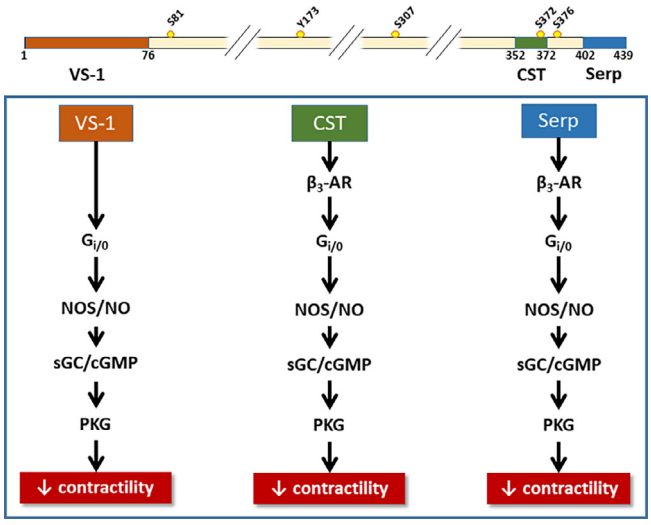

Fig. 3. Oversimplified scheme of human full-length CgA. The position of VS-1, CST and Serp is illustrated. Yellow circles indicate phosphorylation sites. The lower panel illustrates the involvement of the Gi/o/NO/cGMP/PKG pathway in the reduction of contractility induced by VS-1, CST and Serp on the fish heart. Please note that human VS-1 and bovine CST were used on eel cardiac preparations, while mouse Serp was used on the goldfish heart. The role of β_3-AR in mediating the cardiomodulation induced by CST and Serp is also shown. For ref. and details see the text.

tested. For example, in the eel, the negative inotropism elicited by VS-1 and CST involves $G_{i/0}$ proteins and the NO/cGMP/PKG pathway (Table 1; Fig. 3). This differs from the mechanism described in the frog heart in which the CgA_{7-57} synthetic peptide elicited cardio-inhibition resulted independent from $G_{i/0}$ proteins, and the NO-dependent pathway (Corti et al., 2002; Corti et al., 2004). Moreover, the pGlu-Serp-dependent depression of mechanical performance enrolles the NO-cGMP-PKG signal transduction pathway both in teleosts (*C. auratus*) and amphibians (*Rana esculenta*), while occurred *via* Endothelin-1 type B receptors (ETBR) in frog and β_3-ARs in goldfish (Imbrogno et al., 2017).

The above data suggest that the CgA fragments use apparently redundant strategies for cardiac control, whose biological significance remains unclear. In fact, by acting on either overlapping or different sites, they may elicit either summation and synergism, or potentiation of the target responses (Imbrogno et al., 2004, 2010, 2017,; Tota et al., 2004; Mazza et al., 2010). Likewise, in mammals, the cleavage of proANF gives rise to the major form of circulating ANP (ANP1-28), plus several biologically active peptides (proANF1-30, long-acting sodium stimulator; proANF31-67, vessel dilator; proANF79–98, kaliuretic stimulator) (Vesely et al., 1994). At least two of them, i.e. vessel dilator and ANP, show overlapping properties, being vasodilatory, diuretic and natriuretic (Vesely, 2006). This suggests that in teleosts, as well as in mammals, the processing of cardioactive peptides from the same prohormone may be advantageous in maintaining homeostasis.

Table 1
Cardiac effects and mechanism of action of CgA-derived peptides in the eel (*A. anguilla*) (ND = Not Detected).

	Basal performance	Adrenergic stimulation	Frank-Starling response	Major signalling	Refs.
VS-1	Negative inotropism	Anti-adrenergic	ND	Ca^{2+} and K^+ channels, EE-NO-cGMP cascade, cytoskeleton	Imbrogno et al. (2004), Tota et al. (2004), Mazza et al. (2007), Mazza et al. (2010)
VS-2	Negative inotropism	Anti-adrenergic	ND	ND	Imbrogno et al. (2004)
CgA_{7-57}	Negative inotropism	Anti-adrenergic	ND	Ca^{2+} and K^+ channels	Imbrogno et al. (2004) Tota et al. (2004)
CST	Negative inotropism	Anti-adrenergic	Stimulation	β_3-AR-Gi/o-NO-cGMP cascade	Imbrogno et al. (2010)
Serpinin	Negative inotropism	ND	ND	β_3-AR-Gi/o-NO-cGMP cascade	Imbrogno et al. (2017)

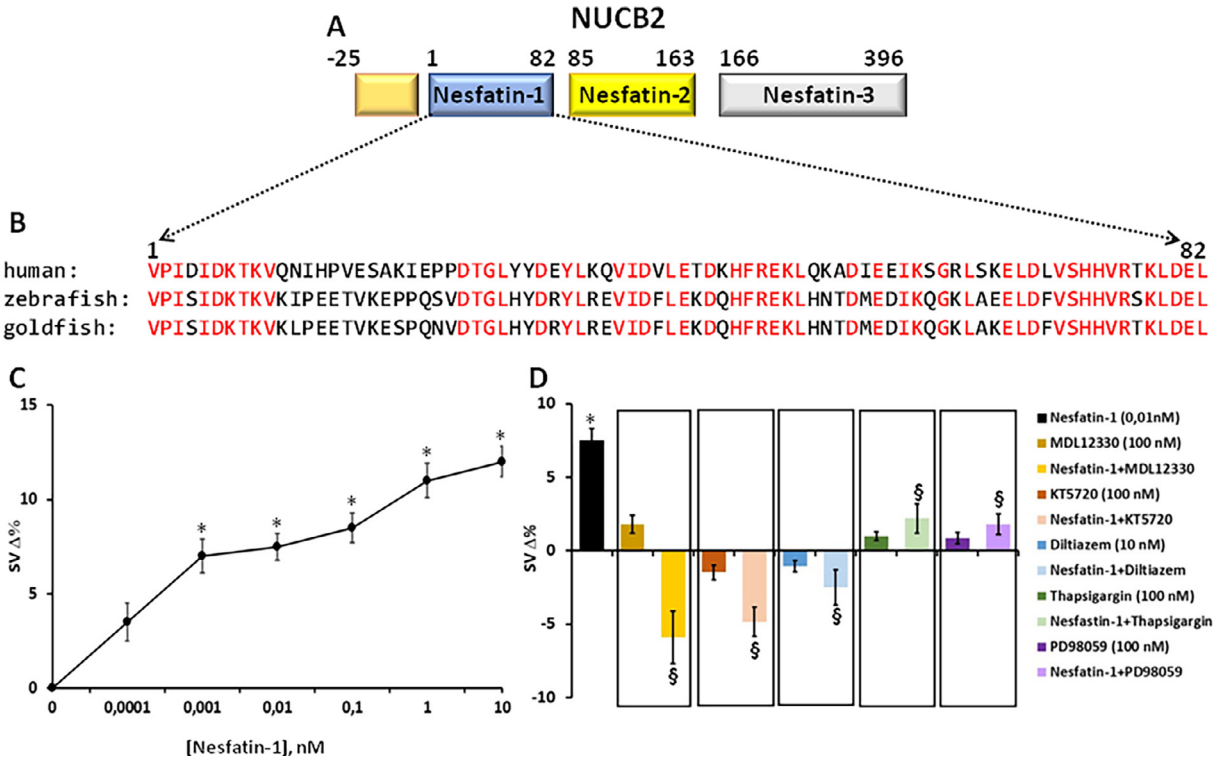

Fig. 4. NUCB2 structure, nesfatin-1 sequences, and cardiac effects of the peptide. (A) NUCB2 structure and the position of the three nesfatin peptides. (B) Nesfatin-1 sequences from human, zebrafish and goldfish (Gonzalez et al., 2010; Imbrogno et al., 2015b); highly conserved amino acids are in red. (C) Dose-response curve of nesfatin-1 on the goldfish heart stroke volume (SV). (D) The effects of adenylate cyclase, PKA, L-type Ca^{2+} channels, SERCA2a and ERK inhibitors (MDL_{12330}, KT_{5720}, Diltiazem, Thapsigargin, PD_{98059}, respectively) on the negative inotropism induced by 0.01 nmol L^{-1} of nesfatin-1 on the goldfish heart are illustrated. Modified from Mazza et al. (2015a,b).

7. Other endocrine Modulators: the role of the appetite-controlling hormone Nesfatin-1

Recent investigations, mainly performed in mammals, established the cardiac role of substances firstly identified for functions other than the control of the cardiovascular system. This is the case of humoral factors known for their central modulation of nutrition and energy balance, but also able to exert direct cardiac effects (see for ref. Imbrogno et al., 2015b). Among these, a peptide recently regarded with interest as a multifunctional hormone, not only in mammals but also in teleost fish, is the hypothalamic 82-aa peptide nesfatin-1 (Imbrogno et al., 2015b).

Nesfatin-1 is an anorexigenic peptide proteolitically derived from the 82-N-terminal residues of the larger protein Nucleobindin 2 (NUCB2) (Oh-I et al. 2006) (Fig. 4). In mammals, nesfatin-1 is expressed, together with the precursor NUCB2, in hypothalamic regions controlling water-food intake, body weight, and glucose homeostasis. The peptide is also peripherally expressed, as shown in the rat heart, in which it is present together with NUCB2 (Imbrogno et al., 2015b). In mammals, nesfatin-1 modulates the cardiovascular function *via* a central control of sympathetic and vagal influences on arterial blood pressure and heart rate (Mimee et al., 2012; Yosten and Samson, 2009). Moreover, as shown in the rat heart, it depresses contractility and relaxation, and elicits cardioprotection against ischemia/reperfusion injuries (Angelone et al. 2013). Lastly, like insulin, it affects cardiomyocyte energy metabolism, by increasing glucose uptake (Feijóo-Bandín et al., 2013).

Also in fish, nesfatin-1 represents an appetite regulatory peptide. Nesfatin-1-like-immunoreactive cells have been recently revealed in the hypothalamus, within the nucleus lateralis tuberis and the anterior intestine, J-loop, of the goldfish (*C. auratus*) (Gonzalez et al., 2010). In the goldfish, brain NUCB2 mRNA expression and nesfatin-1 circulating levels decrease upon fasting and increase after meal intake (Gonzalez et al., 2010), clearly suggesting an anorexigenic role. Moreover, in agreement with evidence in mammals (Imbrogno et al., 2015b), in the goldfish, nesfatin-1 appears to be linked to other appetite regulatory peptides, since in brain and gut it co-localizes with ghrelin, and alters ghrelin, cholecystokinin and orexin mRNA expression (Kerbel and Unniappan, 2012). Recently, Mazza and coworkers found that nesfatin-1 is present in various tissues such as brain, gills, intestine and skeletal muscle of the goldfish (*C. auratus)* (Mazza et al., 2015a). Although the goldfish heart does not express nesfatin-1, the direct exposure of the isolated and perfused working heart to the exogenous peptide induces a dose-dependent increase of contractility which involves cAMP, Protein Kinase A (PKA), L-type calcium channels and sarco/endoplasmic reticulum calcium ATPase (SERCA2a) pumps, as well as extracellular signal–regulated kinases1/2 (ERK1/2) and phospholamban (Fig. 4). These results suggest that as in mammals, in teleosts, nesfatin-1 exerts direct cardiac effects that may be additive and/or alternative to a central action of the peptide on brain areas involved in the cardiovascular control.

The goldfish is characterized by an extraordinary ability to face stressful conditions, in particular in severe hypoxia (Bickler and Buck, 2007; Gattuso et al., 2018). Under these conditions, the heart responds by increasing its mechanical performance (Imbrogno et al., 2014). Although not directly analysed in their study, Mazza and coworkers hypothesized that the cardiostimulation induced by nesfatin-1 on the isolated and perfused goldfish heart may contribute to the endogenous mechanisms of stress (i.e. hypoxia) resistance (Mazza et al., 2015a). To this purpose, the involvement of ERK1/2 in the mechanisms of action of nesfatin-1 may be of relevance. In fact, as demonstrated in mammals, this kinase is involved in both short- and long-term responses elicited by many cardioactive substances (Dube et al., 2006; Clerk and Sugden, 2004), and in cardioprotection against stress challenges, including

ischemic damages (Darling et al., 2005).

Several recent evidences report in different tissues of the goldfish *C. auratus* the expression of ghrelin, a peptide well known in mammals for its role in the control of nutrition and metabolism (Blanco et al., 2017). However, to date, information regarding a direct influence of ghrelin, as well as of other appetite-regulating hormones, on fish cardiac function remains lacking.

8. Conclusions

Recent years of cardiovascular research in teleost have provided novel and crucial pieces of information on the humoral circuits that sustain heart homeostasis, allowing at the same time, adaptive plasticity. The lesson derived from this increasing knowledge indicates that in fish the dynamic balance between endocrine substances, receptors, autocrine/paracrine pathways, and their short- and long-term physiological implications exert a multilevel physiological integration, which contributes to heart plasticity. Many gaps are present due to the still discontinuous information. However, examples provided in this review highlight the power of the teleost heart as an experimental model useful to elucidate, from organ to cellular, subcellular and molecular levels, basic mechanisms of the coordinated physiological reactions which support cardiac mechanics.

Ethics

There was no data collection for this review article; it is based entirely on previously published research.

Data accessibility

All data used in this study have been previously published.

Authors' contributions

S.I. led the writing efforts. All authors discussed literature data, and participated in writing and editing the review. M.C.C. developed the figures. All authors gave final approval for publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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