Understanding how stress responses and stress-related behaviors have evolved in zebrafish and mammals

Murilo S. de Abreu a,b,* , Konstantin A. Demin c,d,e , Ana C.V.V. Giacomini a,f , Tamara G. Amstislavskaya g,h , Tatyana Strekalova i , Gleb O. Maslov i , Yury Kositsin d,i , Elena V. Petersen b , Allan V. Kalueff j,k,**

a Bioscience Institute, University of Passo Fundo (UPF), Passo Fundo, RS, Brazil
b Institute of Experimental Medicine, Almazov National Medical Research Center, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia
c Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia
d Granov Russian Scientific Research Center of Radiology and Surgical Technologies, Ministry of Healthcare of Russian Federation, St. Petersburg, Russia
e Postgraduate Program in Environmental Sciences, University of Passo Fundo (UPF), Passo Fundo, RS, Brazil
f Scientific Research Institute of Physiology and Basic Medicine, Novosibirsk, Russia
g Novosibirsk State University, Novosibirsk, Russia
h University of Maastricht, Maastricht, Netherlands
i Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia
j School of Pharmacy, Southwest University, Chongqing, China
k Ural Federal University, Ekaterinburg, Russia
l Neuroscience Program, Sirius University, Sochi, Russia

** Corresponding author. Bioscience Institute, University of Passo Fundo, Passo Fundo, Brazil.
** Corresponding author. School of Pharmacy, Southwest University, Chongqing, China.
E-mail addresses: abreu_murilo@hotmail.com (M.S. de Abreu), avkalueff@gmail.com (A.V. Kalueff).

A R T I C L E   I N F O

Keywords:
Zebrafish
Rodents
Cortisol
Stress axis
Behavior
Animal models

A B S T R A C T

Stress response is essential for the organism to quickly restore physiological homeostasis disturbed by various environmental insults. In addition to well-established physiological cascades, stress also evokes various brain and behavioral responses. Aquatic animal models, including the zebrafish (Danio rerio), have been extensively used to probe pathobiological mechanisms of stress and stress-related brain disorders. Here, we critically discuss the use of zebrafish models for studying mechanisms of stress and modeling its disorders experimentally, with a particular cross-taxon focus on the potential evolution of stress responses from zebrafish to rodents and humans, as well as its translational implications.

1. Introduction

Stress response is a complex set of physiological reactions that aim to restore body homeostasis disturbed by various environmental insults by activating the sympatho-adrenomedullary system (SAM) and the hypothalamic-pituitary-adrenal axis (HPA) (Russell and Lightman, 2019; Wendelaar Bonga, 1997b). Stress affects human and animal central nervous system (CNS) via multiple mechanisms (Carlson and Rosser-Hogan, 1991; Johansson et al., 2010; Lee et al., 2015; Resnick et al., 2003), including dysregulated neurotransmitters, hormones and expression of key brain genes (Conrad, 2008; McGonigle, 2014; Russell and Lightman, 2019). While normal stress responses are fundamental for organismal survival, pathological stress can be detrimental, causing various brain illnesses, such as anxiety, depression and post-traumatic stress disorder (PTSD) (Cohen et al., 2007; Cohen and Williamson, 1991; McEwen and Stellar, 1993).

Animal models, especially rodents, have been extensively used to study neural mechanisms of stress and stress-related neuropathology (Campos et al., 2013; de Abreu et al., 2021; Patchev and Patchev, 2006; Spagnoli et al., 2016). In addition to mammals, the zebrafish (Danio rerio) and other fishes have demonstrated high relevance to modeling stress responses in vivo (Demin et al., 2020; Spagnoli et al., 2016), as they possess an evolutionarily conserved hypothalamic-pituitary-interrenal (HPI) stress axis that is structurally and functionally homologous to the mammalian HPA axis (Al sop and Vijayan, 2008, 2009). Fishes also have a generally similar brain architectonics (Wullimann et al., 1996) (Fig. 1),

https://doi.org/10.1016/j.ynstr.2021.100405
Received 9 February 2021; Received in revised form 12 September 2021; Accepted 27 September 2021
Available online 29 September 2021
2352-2895/© 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license
(http://creativecommons.org/licenses/by-nc-nd/4.0/).
with multiple shared neurotransmitters and hormones involved in stress responses, between the two taxa (Panula et al., 2010). Here, we evaluate the developing utility of zebrafish models for studying mechanisms of stress and stress-related disorders, with a particular focus on the evolution and translational relevance of stress responses in fish and rodents.

2. Physical and psychological stress responses in fishes, rodents and humans

Stress responses in vivo generally vary based on the type of stressors (physical or psychological) applied. In mammals, psychological stress (e.g., aversive environmental stimuli or predator-related cues) and physical stress (e.g., hemorrhage or infection) engage distinct neural and cellular networks in the brain (Dayas et al., 2001; Godoy et al., 2018). For instance, physical stressors are mainly processed by mammalian brainstem and hypothalamic regions (Dayas et al., 2001; De Kloet et al., 2005; Fenoglio et al., 2006; Ulrich-Lai and Herman, 2009), where the SAM system provides rapid behavioral adaptations, such as alertness, vigilance and appraisal of the situation (De Kloet et al., 2005; Joëls and Baram, 2009). The HPA axis becomes activated later through the brainstem, with the paraventricular nucleus (PVN) of the hypothalamus activating or inhibiting this axis (De Kloet et al., 2005; Joëls and Baram, 2009). The HPA axis becomes activated later through the brainstem, with the paraventricular nucleus (PVN) of the hypothalamus activating or inhibiting this axis (Ulrich-Lai and Herman, 2009). Physical stressors also activate other brain structures that regulate autonomic stress responses, including nucleus of the solitary tract (NTS) and dorsomedial hypothalamus (DMH) (Geerling et al., 2010). The key brain regions involved in physical stressors also include the amygdala, the hippocampus and the prefrontal cortex (PFC) that receive inputs from cortical and subcortical areas, whose outputs converge to subcortical relay sites, hence enabling downstream processing of limbic information (Ulrich-Lai and Herman, 2009).

Psychological stressors can elicit strong physiological, behavioral and cognitive responses in humans (Skoluda et al., 2015) and rodents (Finnell et al., 2017; Pryce and Fuchs, 2017). Together with the prosencephalic nuclei, limbic circuits (the amygdala, the hippocampus, PVN, the ventral tegmental area and the nucleus accumbens) modulate psychological stress in mammals (Russo and Nestler, 2013; Ulrich-Lai and Herman, 2009). The PFC is also important for stress responses (Riederinkhof et al., 2004), as bilateral lesions of the prelimbic cortex (PLC) in rodents increase plasma level of the adrenocorticotrophic hormone (ACTH), corticosterone and the PVN expression of Fos protein (Diorio et al., 1993; Figueiredo et al., 2003b). In contrast, lesioning the infralimbic cortex (ILC) reduces corticosterone secretion, suggesting that PLC and ILC may play opposite roles in responses to psychological stressors (Sullivan and Gratton, 1999). Mammalian PFC also projects to the amygdala, forming a corticolimbic circuit critical for processing both emotional (Gabbott et al., 2005; LeDoux, 2007) and physical (e.g., restraint) stress (Cullinan et al., 1995; Janak and Tye, 2015).

Glucocorticoids, including human or fish cortisol and rodent corticosterone, are biosynthesized and released during stress, to reach their target organs (Joëls et al., 2018; Sadoul and Geffroy, 2019). The biological effects of these stress hormones are mediated by mineralocorticoid (MR) and glucocorticoid (GR) receptors (Katsu and Iguchi, 2016;
gamma (IFN-IL-1) air exposure) show unaltered brain gene expression for interleukins hypothalamus (De Kloet et al., 2005; Russell and Lightman, 2019). As such as the alarm substance or conspecific blood exposure (Abreu et al., 2017). For example, physical stressors like acute net chasing cause stronger cortisol release in zebrafish than do psychological stressors, (De Kloet et al., 1997b), with similar neurochemical and neuroendocrine mechanisms to those in mammals (Table 1). A small freshwater teleost like other vertebrates, various fish species display robust physiological and behavioral stress responses (Schreck and Tort, 2016; Wendelaar Bonga, 1997b), with similar neurochemical and neuroendoctrine mechanisms to those in mammals (Table 1). A small freshwater teleost fish, the zebrafish has rapidly become a powerful novel model system in stress neuroscience research (de Abreu et al., 2021; Demin et al., 2020; Kaluseff et al., 2014a; Stewart et al., 2014). Social isolation for 15 min, an enzyme lacking in rodents (Galloy-Payet and Battista, 2011). As bright light, vortex, shallow water and restraint) upregulates brain mRNA expression of all these genes (Yang et al., 2020). Taken together, these findings demonstrate that stress responses in both fish and mammals are physiologically similar (and, hence, seemingly evolutionarily conserved), especially since they are both directly (and in a similar manner) influenced by the type, intensity, frequency and duration of stress.

Similar to mammalian HPA axis, stress also activates the fish HPI axis to trigger the hypothalamus (especially nucleus preopticus, NPO, homologous to the mammalian PVN) to initiate CRH/ACTH cascade-stimulated synthesis and release of cortisol by the interrenal tissue (Sumpter et al., 1994; Wendelaar Bonga, 1997b). Released by NPO, CRH also stimulates the secretion of proopiomelanocortin (POMC) in the fish anterior pituitary, reaching it via direct projections from NPO (Lederis et al., 1994). POMC is an evolutionary conserved polypeptide expressed in fishes (Arends et al., 1998; Gonzalez-Nunez et al., 2003), rodents and humans (Chang et al., 1980), that acts as a precursor for ACTH, as well as \( \alpha \) - and \( \beta \)-melanocyte-stimulating hormone (MSH). Like in mammals, fish ACTH is the primary hormone responsible for stimulating cortisol secretion (Wendelaar Bonga, 1997b) and controlling its biosynthesis via the melanocortin receptor 2 (MC2R) (Roebuck et al., 1984; Schioth et al., 1996). Produced cortisol is next released into the circulation where its effects on fish target organs, like in mammals, are modulated by MRs and Grs (Pippal et al., 2011; Schaaf et al., 2008).

In addition to glucocorticoids, stress also triggers catecholamine release from fish chromaffin cells, with a rapid rise in blood glucose (Barton and Iwama, 1991; Randall and Ferry, 1992; Wendelaar Bonga, 1997b), as well as epinephrine and norepinephrine (Eto et al., 2014; Nikinmaa, 1992). Stressors can also indirectly modulate brain neurotransmitters (Wendelaar Bonga, 1997b), such as serotonin and dopamine and its metabolites, since zebrafish acutely isolated for 24 h exhibit increased serotonin and reduce its metabolite 5-hydroxyindoleacetic acid (5HIAA) levels, as well as dopamine and its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) (Shams et al., 2017). In addition to altered monoaminergic system, fish chromaffin cells also respond less to cholinergic stimulation following a prolonged physical stress (Reid and Perry, 1994). As fish share a high genetic homology of stress-related genes with their human and rodent analogs (i.e., estimated as 62–64% genetic sequence homology in zebrafish vs. humans and mice, Table 2), several other shared aspects of stress responses will be analyzed further, and compared across the three species.

In addition to physiological and genetic similarities discussed above, some interesting differences in neurobiology of zebrafish vs. mammalian stress responses also exist. For example, exposure of zebrafish to chronic stress increases brain BDNF levels (Song et al., 2018), which are usually reduced (in most, but not all, brain areas) by chronic stress in rodents and humans (Karege et al., 2002; Licinio and Wong, 2002; Radahmadi et al., 2015), as well as in patients with affective disorders, such as PTSD, anxiety and depression (Bremner et al., 2000; Chen et al., 2006; Duman and Monteggia, 2006; Mervaala et al., 2000). In contrast, the over-expression of brain BDNF evokes anxiolytic and antidepressant effects in rodents (Delheil et al., 2009; Gourley et al., 2008), with a similar therapeutic effect observed following a BDNF augmentation clinically (Brunoni et al., 2008; Zhou et al., 2017). The latter difference may result from a generally higher neuroprotective potential of fish (vs. potentially more ‘fragile’ mammalian) CNS, which may also play a role during stress. Another physiological difference concerns corticosteroid hormones utilized by rodents, humans and fish for their stress responses: while humans and zebrafish utilize cortisol (and laboratory rodents do show some cortisol activity as well) (Bhat et al., 2007; Gong et al., 2015; Hawley and Keevil, 2016; Kulle et al., 2013), the major stress corticosteroid in reptiles, birds and laboratory rodents is corticosterone (Nussey and Whitehead, 2001; Raff et al., 2011; Sadoul and Geffroy, 2019; Usa et al., 2007). In zebrafish and humans, cortisol is produced in the adrenal gland during stress by 17a hydroxylase, CYP17 (Wang and Ge, 2004), an enzyme lacking in rodents (Galloy-Payet and Battista, 2011). As

| Acute stress response | Species | Increased cortisol levels | References |
|-----------------------|---------|---------------------------|------------|
| Alarm substance of conspecifics (15 min) | Zebrafish (Danio rerio) | Whole-body | de Abreu et al. (2017) |
| Social isolation for 15 min | Zebrafish | Whole-body | Kaluseff et al. (2014a) |
| Net chasing (2 min) | Zebrafish | Whole-body | de Abreu et al. (2014) |
| Net chasing (for 1 min) | Jundia (Rhadamia quelen), Nile tilapia (Oreochromis niloticus) | Plasma | Barcellos et al. (1999); Cerciato et al., (2008) |
| Physical restraint (15 min) | Zebrafish | Whole-body | Abreu et al. (2017) |
| Air exposure (1 min) | Zebrafish | Whole-body | Abreu et al. (2015) |
| Repeated electric shock (20 V, 15 mA, 100 Hz for 1 min every 4 min, for 60 min) | Nile tilapia | Plasma | Barreto and Volpato (2006) |
| Acute handling and restraint | Atlantic salmon (Salmo salar) | Plasma | Carey and McCormick (1998) |
| Cold shock (28–18°C) | Matrixia (Brycon amazonicus) | Plasma | Inoue et al. (2008) |
| Aerial emersion handling stressor | Pallid (Scaphirhynchus albus) and hybrid pallidaxtosthenose (S. albusxplatyzeus) sturgeons | Plasma | Barton et al. (2000) |
| Handling (30-s air exposure) | Lake (Salvelinus namaycush), Rainbow (Oncorhynchus mykiss), brown (Salmo trutta) and brook trout (Salvelinus fontinalis) | Plasma | Barton (2000) |
| Transportation for 2h | Lake, rainbow, brown and brook trout | Plasma | Barton (2000) |

McEwen et al., 2015; Pippal et al., 2011; Schaaf et al., 2008) that are co-expressed particularly abundantly in the limbic neurons (De Kloet et al., 2005; Herman et al., 2003; Joëls et al., 2012). Glucocorticoids are also responsible for biofeedback inhibition of ACTH secretion from the pituitary and corticotropin-releasing hormone (CRH) secretion from the hypothalamus (De Kloet et al., 2005; Russell and Lightman, 2019). As MRs are implicated in the appraisal and the onset of stress response, GRs (with a ~10-fold lower affinity for corticosteroids) are activated by high levels of these hormones (Reul and Kloet, 1985) and directly affect synaptic transmission, plasticity, learning, and memory (Finsterwald and Alberini, 2014), in addition to modulating multiple other (e.g., metabolic and immune) physiological systems (De Kloet et al., 2005).

Like other vertebrates, various fish species display robust physiological and behavioral stress responses (Schreck and Tort, 2016; Wendelaar Bonga, 1997b), with similar neurochemical and neuroendoctrine mechanisms to those in mammals (Table 1). A small freshwater teleost fish, the zebrafish has rapidly become a powerful novel model system in stress neuroscience research (de Abreu et al., 2021; Demin et al., 2020; Kaluseff et al., 2014b; Stewart et al., 2014). Similar to mammals, fish also display distinct, type-specific stress responses (Demin et al., 2020; Khan et al., 2017). For example, physical stressors like acute net chasing cause stronger cortisol release in zebrafish than do psychological stressors, such as the alarm substance or conspecific blood exposure (Abreu et al., 2017). While zebrafish acutely subjected to a mild stressor (e.g., 1-min air exposure) show unaltered brain gene expression for interleukins (IL-1β and IL-6, brain-derived neurotrophic factor (BDNF), interferon gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) (Kirsten et al., 2020), a more severe acute stress (e.g., a 90-min exposure to cold water, Table 1.)
such, some species differences in stress neuroendocrinology may play a role in how fish and rodents respond to acute and chronic stressors.

Certain anatomical differences in brain morphology, especially within the limbic system of mammals and fishes (Fig. 1), may also contribute to some variance in physiological and behavioral responses to stress across these species (Herman et al., 2005; Price, 2013). For instance, acute restraint stress, a common stress protocol used to induces stress-related behaviors, differentially affects animal limbic system but not until the fourth week of psychological stress (e.g., witnessing conspecifics experiencing electric foot shock) stress, but not until the fourth week of psychological stress (e.g., witnessing conspecifics experiencing electric foot shock) stress (Li et al., 2019). In rodents, behavioral (e.g., thigmotaxis in the open field test) and molecular (e.g., decreased hippocampal GR expression) effects of such physical stressors appear early, but are relatively moderate, compared to the later-onset, but more pronounced impact of psychological stressors (Li et al., 2019). In zebrafish, while acute exposure to both physical (Ramsay et al., 2009) and chemical (Abreu et al., 2017) stressors in animal models of physical vs. psychical stressors. For example, adult male rats exhibit GR-mediated hippocampal atrophy and behavioral abnormalities on the second week of physical (electric footshock) stress, and cortical amygdaloid nuclei, dorsal raphe, locus coeruleus and brainstem nuclei (Brunoni et al., 2008; Ressler, 2010). It has recently been suggested that rodent stress response may also elicit characteristic self-grooming behavior as part of the ‘fight, freeze, flight or groom’ behavioral tetrad (Song et al., 2016b). While the prominent role of rodent self-grooming behavior and its patterning under stress is being widely recognized (Kalucy et al., 2016b; Song et al., 2016a), and likely represents an evolutionarily conserved trait in multiple species, fishes
Neurobiology of Stress 15 (2021) 100405

5

15-year-old individuals display higher cortisol levels in response to so
2009), and the HPA axis responsiveness varies during puberty, as
(Andresen et al., 2020), thus, making facial expression potentially useful and sen-
sitive biomarker of stress in mammals (also see similar important role of
human facial expression in stress (Mayo and Heilig, 2019). However,
while mammals have a remarkably complex facial muscles (Brecht and
Freiwald, 2012; Burrows et al., 2006), little is known about facial re-
ponses to stress in fishes, clearly meriting further translational studies.

3. Effects of social environment and age on stress in zebrafish and mammals

Social environment is a complex factor modulating rodent (Beery
and Kauper, 2015), human (Santini et al., 2020) and zebrafish behavior
(Fontana et al., 2021). As already mentioned, social deficits, such as early
deprivation, isolation, hierarchy, crowding and social instability,
cause experimental stress in rodents and zebrafish (Beery and Kauper,
2015; Demin et al., 2020). For example, over-crowded zebrafish (40
fish/L) exhibit higher whole-body cortisol than fish maintained at a low
(0.25-fish/L) density (Ramsay et al., 2006). In rodents, crowding acti-
vates the HPA axis and causes social avoidance (Lee et al., 2018), ad-
renal hypertrophy (Christian, 1971) and elevated corticosterone (Brown
and Grunberg, 1995). In zebrafish, social stress can also be modeled by
social isolation, since zebrafish, individually housed for 2 weeks, spend
less time in the bottom of the novel tank (an anxiolytic-like effect)
(Parker et al., 2012) and more time in the center of the open-tank (an
anxiolytic-like effect) (Shams et al., 2015). These socially isolated fish
also display lower baseline cortisol levels (Parker et al., 2012) and
blunted cortisol responses to an acute stressor (e.g., 2-min net chasing),
than group-housed fish (Giacomini et al., 2015). While a short-term
15-min social isolation evokes robust anxiety-like behavioral and
cortisol responses in adult zebrafish (Kaluff et al., 2014a), rodent social
isolation evokes hyperadrenocorticism, reduced body weight, altered
blood composition and enhanced pain responsivity (in females) (Hatch
et al., 1965; Valzelli, 1973), as well as anxiety/fear-like behaviors and poor
social interaction (in males) (Lukkes et al., 2009). Overall, these
findings demonstrate generally similar effects of social factors on the
development of stress responses in zebrafish and mammals.

However, there are also some interesting distinct effects of chronic
social isolation stress between zebrafish, rodents and humans (Fig. 1),
since in mammals it increases the risk of mental disorders (e.g., anxiety)
(Lukkes et al., 2009; Santini et al., 2020), but causes an anxiolytic-like effect in zebrafish (Parker et al., 2012; Shams et al., 2015) (Fig. 1). On
the one hand, these differences may be due to potentially faster adap-
tion to novel environment (e.g., to isolation) and brain modulation (e.
g., altered neurogenesis) in fish compared to mammals (Grandel et al.,
2006; Kaslin et al., 2008). Another potential contributing factor can be
some genetic differences, mostly due to teleost-specific genome duplica-
tion in zebrafish (Howe et al., 2013). For example, while mammals have
two parathyroid hormone (PTH) receptor genes (PTH1R and
PTH2R) vs. three in zebrafish (pht1r, pht2r and pht3r) (Gensure et al.,
2004; Hogan et al., 2005), already associated with social isolation effects (e.g., down-regulating pth2 gene in zebrafish (Anneser et al., 2020).

Age also plays an important role in modulating stress responses
(Novais et al., 2017). In both men and women, evening cortisol is higher
in older than younger subjects (Gutchess et al., 2019; Larsson et al.,
2009), and the HPA axis responsiveness varies during puberty, as
15-year-old individuals display higher cortisol levels in response to so-
cial stress than 9-11-year-olds (Gunnar et al., 2009). In rodents,
behavioral impact of stress also differs between ages (Novais et al.,
2017), as adolescent female rats avoid a resident female, whereas adult
females are more active and aggressive (Ver Hoeve et al., 2013).
Adolescent female (but not male) rats exhibit less anxiety following
social defeat stress, but equally high adult anxiety in both sexes
(McCormick et al., 2008). Paralleling mammalian age-specific data,
acute stress (e.g., 30-s air exposure) unables anxiety-like behavior and
whole-body cortisol in young (Aponte and Petrunich-Rutherford, 2019),
but not adult zebrafish (Tran et al., 2014; Tran and Gerlai, 2015). Age
also influences zebrafish locomotor activity, as aging 18-month old
zebrafish are more immobile than young (6–9-months old) fish in the
novel tank test (Evans et al., 2021). Collectively, this suggests that age
gradually, and generally in a rather similar manner, impacts zebrafish,
rodents and human stress responses.

Interestingly, some age aspects of the three model species may also
factor into differential shaping of their stress responses. For example,
humans become adults at the age of 20, old at 65, and live ~80 years
(Wilson et al., 2019). Laboratory mice are considered adults at 2 months,
old at 1.5–2 years, and have a lifespan of 2.5–3 years (Flurkey and
Harrison, 2007), whereas laboratory zebrafish become young adults at
the age of 3 months, old at 30 months, and live ~4 years (Kishi et al.,
2009). As such, humans have a shorter adulthood (75% of the respective
lifespan), compared 83% in mice and especially 94% in zebrafish. The
duration of ‘mature’ adulthood (from adult to old) also varies, ranging
from ~56% in humans and mice to 63% in zebrafish. Likewise, humans
seem to have relatively shorter old age (20%), compared to mice (33%)
and zebrafish (38%). The latter aspects, in turn, may underlie potential
species differences in stress responses. For example, this may hypo-
thetically render humans more vulnerable to stress (than mice and
zebrafish) by being relatively more exposed to early-life stressors. At
the same time, such age structure differences may also provide the three
species with distinct temporal opportunities for coping, e.g., making
zebrafish relatively more stress-resistant by ‘extending’ the life period
when their brain is mature and can therefore most efficiently cope with
stress, compared to mammals. Clearly, these features merit further scrutiny and further cross-species analyses.

4. Sex differences in stress responses in zebrafish, rodents and humans

Sex differences are increasingly reported in response of acute or
chronic stressors exposure in zebrafish, rodents and humans. For
example, unpredictable chronic stress lowers aggression and whole-
body cortisol in female zebrafish (Rambo et al., 2017), but shows no
differences in baseline cortisol levels between the sexes (Wong et al.,
2019). In salmonids, plasma cortisol is higher in females vs. males (Idler
and Freeman, 1968), whereas female rodents show higher baseline
corticosterone (Bangasser and Wicks, 2017; Handa et al., 1994; Kitay,
1961) and corticosterone responses to stress (Bangasser and Valentino,
2014; Seale et al., 2004) than males. This also parallels clinical data on
higher baseline cortisol in women (Larsson et al., 2009), who are also
more likely to develop serious stress-related disorders, including anxi-
ety, depression and PTSD (Hu et al., 2017; McLean et al., 2011; Patten
et al., 2006).

While crowding stress particularly strongly affects male mammals, it
is either calming or inactive in females (Brown and Grunberg, 1995;
Kotrschal et al., 2007). In rodents, even when the same event is stressful
to both males and females, the sequelae of stress exposure may differ, for
example, impairing classical conditioning in females, but improving in
males (Wood and Shors, 1998). The most prominent model of rodent
social stress is the social defeat, typically induced in a resident-intruder
test where a test subject is paired with a dominant resident (Martinez
et al., 1998). Some sex differences have also been observed in this rodent
model (Steinman and Trainor, 2017), as both sexes show similar rates of
freezing when confronted with an aggressive resident, yet females make
more attempts to flee (Trainor et al., 2013). As zebrafish dominance is
associated with a greater body size and aggression, dominant males are
generally more aggressive than dominant females (Paul et al., 2010).
While male zebrafish over-express whole-brain cfr (Evans et al., 2021),
adult females display higher locomotion after repeated daily stress
Neurobiology of Stress 15 (2021) 100405

Individual differences strongly impact biological and behavioral stress responses, forming resilient and vulnerable groups (Heinzelmann and Gill, 2013). Vulnerable subjects poorly adjust to stressors and express inappropriate responses, while resilient subjects distinguish the adversity as less stressful, and employ adaptive behavioral and physiological responses (Franklin et al., 2012). For example, human subjects who secrete a greater amplitude of cortisol diurnally demonstrate lesser limbic activation (e.g., amygdala, hippocampus and hypothalamus) when exposed to stressful video images (Cunningham-Bussel et al., 2009). While C57BL/6J mice subjected to chronic social defeat can be separated into susceptible and resilient individuals based on their social interaction scores (Krishnan et al., 2007), selectively bred outbred Roman high- (RHA) and low-avoidance (RLA) rat sub-strains differ (RLA > RHA) in stress-evoked ACTH and corticosterone responses (Steimer and Driscoll, 2005). Similar to mammals, fishes exhibit pronounced intraspecies variability in stress responses (Demin et al., 2019; Volgin et al., 2019). For instance, less aggressive zebrafish with a reactive stress coping style display higher whole-body cortisol peaks than their bolder, proactive counterparts (Wong et al., 2019). Individually in zebrafish locomotion (e.g., high vs. low activity) is associated with differences in stress-related phenotypes, as female high-activity fish are less anxious than low-activity females (Tran and Gerlai, 2013). In addition, zebrafish also present individual differences in risk-taking behavior (e.g., predator inspection) between shy and bold individuals (Dugatkin et al., 2005). Collectively, this suggests a general conservation of stress resilient and vulnerability phenotypes across zebrafish and mammals. However, the exact evolutional role of such intraspecies variability remains unclear, and necessitates further studies. For instance, translational models of stress may benefit from targeting ‘core’ genetic and molecular elements of resilience/vulnerability phenotype represented simultaneously in all species. At the same time, recent study revealed no similarities between zebrafish, Atlantic salmon (Salmo salar) and European sea bass (Dicentrarchus labrax) in transcriptomic signatures of their proactive behavior, highlighting some complication of cross-species studies of individual differences (Planellas et al., 2020).

There are also well-established strain and population differences in human stress responses (Miller and Kirschbaum, 2019). For instance, US and North European human subjects show lower cortisol stress responses and more severe depression then in some other European countries (e.g., Italy and Germany) (Kessler et al., 2015; Miller and Kirschbaum, 2019). Immobilization stress increases acoustic startle in Sprague–Dawley, but not Long–Evans rats (Faraday, 2002), whereas Fisher-344 rats show stress-related anhedonia, unlike more resilient Lewis rats (Ergang et al., 2015). Likewise, BALB/cj mice are more vulnerable to stress, compared C57BL/6J (Razzoli et al., 2011) or SWR/J mice (Szklarczyk et al., 2012). In zebrafish, overt strain differences in stress responsivity also exist. For example, leopard, albino, AB and especially wild-derived strains considered to be highly sensitive to stress factors, whereas Tüpfel long-fin (TL) and wild-type short-fin zebrafish are more resilient (Egan et al., 2009a; Kaluβeff et al., 2016a; Seguret et al., 2016; van den Bos et al., 2017a; van den Bos et al., 2017b; Vignet et al., 2013). The AB and TL zebrafish also differ in HPI axis activity (e.g., higher brain cf1, gr-beta, bdnf, pcam, neurod1, cart4, igf1 and soc3c expression) in both larvae and adult AB zebrafish (Gorissen et al., 2015; van den Bos et al., 2017a).

Laboratory zebrafish strains also differ markedly in behavior and stress responses from wild-caught or wild-derived (e.g., WIK) fish populations (Collier et al., 2017; Kaluβeff et al., 2016a). For instance, laboratory strain (e.g., TAB line) is less sensitive to stress evoked by a conspecific alarm substance exposure than wild (Ogwang, 2008). Leopard and albino strains present a high-anxiety in the novel tank test than wild-type zebrafish (Egan et al., 2009b). In addition, AB zebrafish had higher basal whole-body cortisol and lower inhibitory avoidance and shoal cohesion than TL zebrafish (Gorissen et al., 2015). Overall, these findings demonstrate that individual and strain differences in CNS stress responses are also seen across species, likely representing yet another shared, evolutionarily conserved aspect of animal stress responsivity.

6. Epigenetic modulations of stress response

In addition to physiological and CNS responses discussed above, stress also involves various epigenetic processes (e.g., DNA methylation, histone modification and microRNA activity) in the brain (Badyaev, 2005; Demin et al., 2020; Stankiewicz et al., 2013). For instance, human childhood trauma increases methylation of NR3CI (nuclear receptor subfamily 3 group member 1) gene (Van Der Knaap et al., 2014), whereas acute rodent predator stress increases the number of hippocampal neurons with phosphorylated serine 10 of histone 3 (H3) (Bilang-Bleuel et al., 2005). Acute restraint in rodents increases brain tri-methylation of H3 lysine 9 and reduces mono-methylation and tri-methylation of H3 lysine 27 (Hunter et al., 2009). Rodent chronic social defeat increases the acetylation of H3 lysine 9 and lysine 14 in neurons and glial (Hinwood et al., 2011), while chronic stress lowers medial PFC DNA methyltransferase 3a (Dnmt3a) mRNA expression, and hence a global DNA methylation (Elliot et al., 2016).

Zebrafish also represent a useful tool for studying brain epigenetic regulation during stress (Lakstsygal et al., 2018). For instance, zebrafish exposure to acute severe stress upregulates CNS expression of several epigenetic genes, including dnm3ta, and dmnt3b, h4at1 (histone acetyltransferase 1) and hdc4 (histone deacetylase) genes 10 days post-exposure (Yang et al., 2020). Paralleling this stress-induced up-regulation of zebrafish hdc4, adult rats exposed to a single prolonged stressor (e.g., 2-h restraint + 20-min forced swim stress) also increase the number of HDAC4-expressing PFC and hippocampal neurons (Sailaja et al., 2012; Zhang et al., 2020). Taken together, these findings suggest that some epigenetic mechanisms induced by stress (e.g., upregulation of HDAC4 by acute stressors) are similar across zebrafish and mammals, and hence may represent core, evolutionarily conserved molecular aspects of stress regulation in vertebrate CNS.

Notably, stress responsivity is also modulated transgenerationally. For example, parental life events impact behavior of rodent offspring, since F1 from restrained (for 60 days) mothers and/or fathers show lower anxiety and serum cortisol and increased hippocampal mRNA expression of GR and BDNF than control F1 offspring from unstrressed parents (He et al., 2016). Similar behavioral and molecular changes are also observed in F2 rodents (He et al., 2016). In humans, maternal cortisol affects the HPA axis function of the child, and may evoke their stress-related disorders later in life (Davis et al., 2007; Karlen et al., 2013; Oberlander et al., 2008). Similarly, maternal cortisol may also regulate the development of the fish HPI axis, subsequently impacting larval stress response (Nesan and Vijayan, 2016), because the role of maternal cortisol in neurogenesis and behavior of larval zebrafish has already been reported (Best et al., 2017). In zebrafish, larvae exposed for 6 days to fluoxetine (a selective serotonin reuptake inhibitor, SSRI) demonstrate lower cortisol levels in response to an acute stressor (e.g., net handling stressor) when adult (Vera-Chang et al., 2018). In addition, the suppression of stress response by fluoxetine persists for three consecutive generations in the unexposed descendants (Vera-Chang et al., 2018). Collectively, these findings demonstrate that while zebrafish (with an ex-uterus development) differ in developmental biology from mammals, behavioral and physiological effects of
parenteral exposure to stress or drugs and their transgenerational consequences may be rather similar to mammals.

7. Conclusion

Mounting evidence summarized here, including homologous stress-related genes (Table 2), similar behaviors, overlapping brain anatomy (Fig. 1, Table 3) and shared epigenetic modulation, supports common, evolutionarily conserved mechanisms of various CNS stress responses in fish and mammals. Recognizing such common natural evolution across vertebrate taxa, our understanding how stress response has evolved in fish and mammals may be rather similar to mammals.

7. Conclusion

Mounting evidence summarized here, including homologous stress-related genes (Table 2), similar behaviors, overlapping brain anatomy (Fig. 1, Table 3) and shared epigenetic modulation, supports common, evolutionarily conserved mechanisms of various CNS stress responses in fish and mammals. Recognizing such common natural evolution across vertebrate taxa, our understanding how stress response has evolved in fish and mammals may be rather similar to mammals.
Cohen, S., Williamson, G.M., 1991. Stress and infectious disease in humans. Psychol. Rev. 98, 5258.

Cohen, S., Janicki-Deverts, D., Miller, G.E., 2007. Psychological stress and disease. Jama 298, 1152–1159.

Chen, Z.-Y., Jing, D., Bath, K.G., Ieraci, A., Khan, T., Siao, C.-J., Herrera, D.G., Toth, M., Chang, A.C., Cochet, M., Cohen, S.N., 1980. Structural organization of human genomic DNA encoding the pro-opiomelanocortin peptide. Proc. Natl. Acad. Sci. U. S. A. 77, 4890–4894.

Chen, Z.-Y., Jing, D., Bath, K.G., Ieraci, A., Khan, T., Siao, C.-J., Herrera, D.G., Toth, M., Yang, C., McEwen, B.S., Hempstead, B.L., Lee, F.S., 2006. Genetic variant BDNF DNA encoding the pro-opiomelanocortin peptide. Proc. Natl. Acad. Sci. U. S. A. 77, 4890–4894.

Chang, A.C., Cochet, M., Cohen, S.N., 1980. Structural organization of human genomic DNA encoding the pro-opiomelanocortin peptide. Proc. Natl. Acad. Sci. U. S. A. 77, 4890–4894.

Chen, Z.-Y., Jing, D., Bath, K.G., Ieraci, A., Khan, T., Siao, C.-J., Herrera, D.G., Toth, M., Yang, C., McEwen, B.S., Hempstead, B.L., Lee, F.S., 2006. Genetic variant BDNF DNA encoding the pro-opiomelanocortin peptide. Proc. Natl. Acad. Sci. U. S. A. 77, 4890–4894.

Chang, A.C., Cochet, M., Cohen, S.N., 1980. Structural organization of human genomic DNA encoding the pro-opiomelanocortin peptide. Proc. Natl. Acad. Sci. U. S. A. 77, 4890–4894.

Chen, Z.-Y., Jing, D., Bath, K.G., Ieraci, A., Khan, T., Siao, C.-J., Herrera, D.G., Toth, M., Yang, C., McEwen, B.S., Hempstead, B.L., Lee, F.S., 2006. Genetic variant BDNF DNA encoding the pro-opiomelanocortin peptide. Proc. Natl. Acad. Sci. U. S. A. 77, 4890–4894.
Katsy, Y., Iyiguchi, T., 2016. Subchapter 95D - Cortisol. In: Takei, Y., Ando, H., Tsutsui, K. (Eds.), Handbook of Hormones. Academic Press, San Diego, 533-e595D-532.

Kendler, K.C., Sampson, N.A., Berglund, P., Graber, M.J., Al-Mahamadi, A., Andrade, L., Bunting, B., Demnyteneca, K., Florescu, S., De Girolamo, G., 2015. Anxious and non-anxious major depressive disorder in the world health organization mental health world surveys. Epidemiol. Psychiatri. Sci. 24, 210-226.

Khan, M., Collier, D.A., Kolter, A.V., Kolesnikov, S.L., Kolenikova, T., Morzhin, V.Y., Warnick, J.E., Kalauke, A.V., Echevarria, D.J., 2017. Zebrafish models in neuropsychopharmacology and CNS drug discovery. Br. J. Pharmacol. 174, 1593-1644.

Kirsten, K., Pomerzaia, A., Koosgoki, G., Mendoza-Soares, S., da Costa, R.A., Maffi, V.C., Krezet, L.C., Barcellos, L.J.G., 2020. Acute and chronic stress differently alter the expression of cytokine and neuronal markers genes in zebrafish brain. Stress 1-6.

Kishan, V., Slack, B.E., Bajwa, S., Zhdanova, I.V., 2013. Zebrafish as a genetic model in biological and behavioral gerontology: where development meets aging in vertebrates—a mini-review. Gerontology 55, 430-441.

Kitay, J.I., 1961. Sex differences in adrenal cortical secretion in the rat. Endocrinology 68, 68-69.

Kotrechal, A., Ilmonen, P., Penn, D.J., 2007. Stress impacts telomere dynamics. Biol. Lett. 3, 128-130.

Krishnan, V., Han, M.H., Graham, D.L., Berton, O., Renthal, W., Russo, S.J., Laplant, Q., Kotrschal, A., Ilmonen, P., Penn, D.J., 2007. Stress impacts telomere dynamics. Biol. Lett. 3, 128-130.

Kulke, A.E., Welzel, M., Holterhus, P.-M., Riepe, F.G., 2013. Implementation of a liquid chromatography tandem mass spectrometry assay for eight adrenal C21 steroids and pediatric reference data. Hormone research in pediatrics 79, 22-31.

Kulke, A.E., Welzel, M., Holterhus, P.-M., Riepe, F.G., 2013. Implementation of a liquid chromatography tandem mass spectrometry assay for eight adrenal C21 steroids and pediatric reference data. Hormone research in pediatrics 79, 22-31.

Lakstygal, A.M., de Abreu, M.S., Kalueff, A.V., 2018. Zebrafish models of epigenetic regulation of CNF functions. Brain Res. Bull. 142, 344-351.

Langford, D.J., Bailey, A.L., Chanda, M.L., Clarke, S.E., Drummond, T.E., Echols, S., Glick, S., Ingrao, J., Klassen-Roux, T., LaCroix-Fralish, M.L., 2010. Coding of facial expressions of pain by laboratory mouse. mSphere. 101, 419-424.

Larsson, C.A., Gallberg, R., Ståhl, L., Lindblad, U., 2009. Salivary cortisol differs with age and sex and shows inverse associations with WHR in Swedish women: a cross-sectional study. BMC Endocr. Disord. 9, 16.

Lederis, K., Fryer, J.N., Maffi, V.C., Schönherr, C., Richter, D., 1994. 2 Corticotropin-Releasing Factors Acting on the Fish Pituitary: Experimental and Molecular Analysis. In: Sherwood, N.M., Hew, C.L., Farrell, A.P., Randall, D.J. (Eds.), Fish Physiology. Academic Press, pp. 67-100.

LeDoux, J., 2007. The amygdala. Curr. Biol. 17, R868-R875.

LeDoux, J., 2007. The amygdala. Curr. Biol. 17, R868-R875.

Lee, Y., Qin, J., Yan, J., Zhang, N., Xu, Y., Zeng, L., Zhu, X., Ju, S., 2019. Differences of physical vs. psychological stress: evidences from glucocorticoid receptor expression, hippocampal subfields injury, and behavioural abnormalities. Brain imaging and behavior 13, 1780-1788.

Lichter, J., Wong, M., 2013. Brain-derived neurotrophic factor (BDNF) in stress and behavioral disorders. Front. Neurosci. 7, 441-453.

Liu, J., Hu, P., Xi, Q.R., Meng, F.T., Zeng, L., Zhou, J., Xu, J., 2019. Influence of emotional stress and the prevalence of digestive diseases. Journal of Pediatric Gastroenterology Nutrition 69, 2511-2519.

Lukkes, J.L., Mokin, M.V., Scholl, J.L., Forster, G.L., 2009. Adult rats exposed to early-life social isolation exhibit increased anxiety and conditioned fear behavior, and altered hormonal stress responses. Horm. Behav. 55, 248-256.

Maeng, L.Y., Milad, M.R., 2015. Sex differences in anxiety disorders: interactions between fear, stress, and gonadal hormones. Horm. Behav. 76, 106-117.

Martinez, M., Calvo-Torrent, A., Pico-Alfonso, M.A., 1998. Sexual and environmental factors on reproductive and fertility in aquatic animals. J. Reprod. Fertil. Suppl. 50, 1-48.

Liu, J., Hu, P., Xi, Q.R., Meng, F.T., Zeng, L., Zhou, J., Xu, J., 2019. Influence of emotional stress and the prevalence of digestive diseases. Journal of Pediatric Gastroenterology Nutrition 69, 2511-2519.

Lukkes, J.L., Mokin, M.V., Scholl, J.L., Forster, G.L., 2009. Adult rats exposed to early-life social isolation exhibit increased anxiety and conditioned fear behavior, and altered hormonal stress responses. Horm. Behav. 55, 248-256.

Maeng, L.Y., Milad, M.R., 2015. Sex differences in anxiety disorders: interactions between fear, stress, and gonadal hormones. Horm. Behav. 76, 106-117.

Martinho, M.C., Pimenta, A.A., Aranha, F.T., Hofmann, S.G., 2011. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. J. Psychiatr. Res. 45, 1027-1035.
