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Towards modeling anhedonia and its treatment in zebrafish

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Abstract

Mood disorders, especially depression, are a major cause of human disability. The loss of pleasure (anhedonia) is a common, severely debilitating symptom of clinical depression. Experimental ==animal== models are widely used to better understand depression pathogenesis, and to develop novel antidepressant therapies. In rodents, various experimental models of anhedonia have already been developed and validated. Complementing rodent studies, the zebrafish (*Danio rerio*) is emerging as a powerful model organism to assess pathobiological mechanisms of affective disorders. Here, we critically discuss the potential of zebrafish for modeling anhedonia and studying its molecular mechanisms and translational implications.

Key-words: zebrafish; antidepressant; behavior; animal models; anhedonia.

Introduction: anhedonia and its experimental models

Affective disorders, especially depression, are a major cause of disability (Steel et al., 2014). While the ability to experience pleasure and interest are essential for human wellbeing (Kent C. Berridge and Kringelbach, 2015), the loss of pleasure (anhedonia) represents a common, severely debilitating clinical symptom of depression (Cooper et al., 2018; De Fruyt et al., 2020). Anhedonia is also highly comorbid with other prevalent psychiatric and neurological disorders, including schizophrenia (Gard et al., 2007; Association, 2013), chronic pain (Garland et al., 2020) and Parkinson's disease (Loas et al., 2012). In humans, anhedonia manifests as losing interest in reward and activities, and spending less time experiencing and pursuing pleasure (American Psychiatric, 2013) (Table 1 and Fig. 1). Deficits in specific neuroanatomical areas (*e.g.*, the prefrontal cortex, dorsal striatum, nucleus accumbens and amygdala (Rizvi et al., 2016; Auerbach et al., 2017)) and neurotransmitter systems (*e.g.,* dopamine, serotonin, opioids, glutamate and gamma-aminobutyric acid, GABA) have been consistently implicated in clinical anhedonia (Barbano and Cador, 2007; van Zessen et al., 2012).

Experimental animal models, especially in rodents, are commonly used to study various aspects of anhedonia (Anisman and Matheson, 2005; Simona Scheggi et al., 2018a). For example, rodent anhedonia-like states can be induced experimentally by unpredictable chronic stress (UCS), social defeat- and early-life stress (Anisman and Matheson, 2005; Simona Scheggi et al., 2018a), often comorbid with anxiety- and depression-like behavior, including behavioral 'despair' (Brockhurst et al., 2015; Olejniczak et al., 2021), motor retardation (hypolocomotion) and social withdrawal (various social deficits) (Frenois et al., 2007; Wilson and Koenig, 2014).

As various experimental manipulations can cause anhedonia-like phenotypes in animals, there are also reliable models to detect and quantify these phenotypes (Table 2).

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Specifically, rodent anhedonia-like states are traditionally assessed in the sucrose preference test (SP, behavioral test based on the animal's natural preference for sweet vs. neutral tastes), conditioned place preference test (CPP, a behavioral paradigm used to study rewarding or aversive properties) and social interaction test (a behavioral assay measuring time spent on social investigation, reflecting the animal's sociability) (Cunningham et al., 2006; Simona Scheggi et al., 2018a). For instance, mice exposed to UCS or repeated social defeat display reduced SP (Strekalova et al., 2004) and social interaction (García-Pardo et al., 2015), whereas rats in the CPP model prefer reward- (e.g., amphetamine)-associated compartment, but not when exposed to UCS (Papp et al., 1991). Likewise, acute or chronic administration of phencyclidine, a non-competitive glutamate N-methyl-D-aspartate NMDA receptor antagonist, induces robust social withdrawal phenotype (Snigdha and Neill, 2008) that can be quantified using rodent social preference and social interaction paradigms (Wilson and Koenig, 2014).

Animal experimental models also emerge as a valuable tool to assess pharmacological rescue of anhedonia (Table 3), as chronic antidepressants relieve rodent anhedonia-like behaviors (Papp et al., 2003; Tsankova et al., 2006). For instance, following chronic stress exposure, vortioxetine, an antidepressant agonist of serotonin 5-HT$_{1A}$ receptors, reduces rat anhedonia (Martis et al., 2021), whereas agomelatine, an antidepressant MT1/MT2 melatonin receptor agonist and 5-HT$_{2C}$ serotonin receptor antagonist, rescues mouse anhedonia (Boulle et al., 2014). Likewise, a 24-h treatment with ketamine, a non-selective NMDA receptor antagonist, causes an antidepressant-like effect in the UCS model and corrects rat anhedonia in the SP test (Jiang et al., 2017).

Anhedonia-like phenotypes can also be induced by various genetic manipulations (Pucilowski et al., 1993; Cinque et al., 2012; Lipina et al., 2013). For example, chronic 4-week UCS decreases SP in the hypercholinergic Flinders Sensitive Line (FSL) rats, a putative genetic

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animal model of depression, vs. more 'resilient' Flinders Resistant Line (FRL) rats (Pucilowski et al., 1993). The Wistar Kyoto rats (WKY, originally bred as normotensive controls for the spontaneous hypertensive SHR rat line) are genetically prone to depression, and also display reduced SP (Wright et al., 2020), whereas juvenile μ-opioid receptor (MOP) knockout mice show anhedonia-like low interest in peers and socially rewarding environment (Cinque et al., 2012). The disrupted-in-schizophrenia-1 (*Disc1*-Q31L) mutant mice also exhibit depression-like behavior, reduced levels of monoamines in the nucleus accumbens, and overt social anhedonia (Lipina et al., 2013). Moreover, environmental manipulations can also be used to induce anhedonia-like phenotypes in rodents (Ashkenazy et al., 2009). For instance, lengthening the light phase from a 12:12-h to a 22:2-h light–dark cycle induces a complex behavioral syndrome in the C3H mice that includes anhedonia in the SP test (Becker et al., 2010). The loss of environmental enrichment (e.g., keeping animals in cages with crinkle paper, metal ladders, and plastic huts) can also elicit an anhedonia-like behavior in female rats (Morano et al., 2019).

Zebrafish models relevant to anhedonia

Complementing rodent models, the zebrafish *(Danio rerio)* has become a valuable model organism to study central nervous system (CNS) pathogenesis (Meshalkina et al., 2017; Fontana et al., 2018), including affective disorders (de Abreu et al., 2018; Konstantin A. Demin et al., 2020a). For example, various aquatic models of chronic stress (Marcon et al., 2016; Cai Song et al., 2018b; K. A. Demin et al., 2020b), social defeat (Nakajo et al., 2020) and early-life stress (Fontana et al., 2020; Fontana et al., 2021a; Hare et al., 2021) have recently been developed and successfully validated in zebrafish. Can these fish display a broader spectrum of evolutionarily conserved CNS traits and, for example, like mammals, develop anhedonia-like phenotypes? Mounting evidence discussed further (Table 4) suggests potential relevance of zebrafish to modeling anhedonia. Here, we critically evaluate the developing utility of

zebrafish models of anhedonia in terms of mechanisms and uses to investigate novel therapies for anhedonia alongside their translational implications.

While rodent models are presently widely used in translational neuroscience and neuropharmacology research, they are relatively time-consuming, expensive and low-throughput (M. Nguyen et al., 2014b). Thus, developing complementary model systems is a critically important strategy to further advance the field. In rodents and humans, stress-induced anhedonia is associated with hypertrophy of medium spiny neurons of the nucleus accumbens, modulation of various neurotrophins, cell adhesion molecules and synaptic proteins (Willner, 2005; Bessa et al., 2009; Christoffel et al., 2011). Importantly, the nucleus accumbens is part of a complex network (receiving glutamatergic, monoaminergic and cholinergic afferents) (Bessa et al., 2013) involved in motivation, reward and reward-seeking behavior (Gold, 2015). In teleost fishes, including zebrafish, a putative homolog of the mammalian nucleus accumbens is the ventral and dorsal telencephalic nuclei, that are rich in gamma aminobutyric acid GABA (Kim et al., 2004) and dopamine receptors (O'Connell et al., 2011), and receive ascending dopaminergic inputs from the putative ventral tegmental area-like homolog (Rink and Wullimann, 2002; P Panula et al., 2010). Zebrafish also share with mammals all major neurochemical (e.g., dopaminergic, serotonergic and cholinergic) pathways (Rink and Wullimann, 2002; Filippi et al., 2010; M. O. Parker et al., 2013a) that are implicated in anhedonia pathogenesis. In general, several models and tests can be directly pertinent to studying anhedonia in zebrafish. One logical approach is to focus on reward-seeking behaviors, aiming to develop assays and tests that characterize deficits in such responses in zebrafish. Indeed, as these fish display a rich behavioral repertoire with a wide range of reward-related behaviors (Kalueff et al., 2013a), reduced reward-seeking behavior can be readily assessed in zebrafish by quantifying their impaired reward-like behavior in CPP and hypophagia models (A. D. Collier and Echevarria, 2013; Michael Nguyen et al., 2014a) (Table 2). In both adult and larvae zebrafish, CPP models assess reward-like phenotypes (Priya Mathur and Guo, 2010; P.

Mathur et al., 2011; Hinz et al., 2013; Adam D. Collier et al., 2014; Daniela Braida et al., 2020), hence reflecting their potential to characterize experimentally induced anhedonia-like states as well. Zebrafish do develop CPP towards a wide range of reward stimuli, including food, warm temperature (Rey et al., 2015) and various drugs, such as morphine, diazepam, fluoxetine, risperidone and buspirone (B. Y. Lau et al., 2011; Abreu et al., 2016). For example, in the CPP test, zebrafish prefer salvinorin A, hallucinogenic drug, and morphine, over drug-free compartment (D. Braida et al., 2007; P. Mathur et al., 2011). However, preference for some rewards is abolished in anosmic zebrafish (Abreu et al., 2016; Abreu et al., 2017), resembling smell loss-induced anhedonia in humans (Keller and Malaspina, 2013).

Social motivation is another powerful drive of human and animal behavior, whose loss can generally trigger anhedonia (Chevallier et al., 2012; Fontana et al., 2021b) (Fig. 1). In fact, social anhedonia is one of the most common and debilitating types of anhedonia seen in clinical depression (Enneking et al., 2019). Importantly, like humans, zebrafish are highly social species (Suriyampola et al., 2016; Fontana et al., 2021b), and are therefore uniquely positioned to generate valuable translational insights into aberrant sociality linked to social anhedonia. Furthermore, multiple behavioral tests have been developed to assess zebrafish social phenotypes (Pham et al., 2012; Asahi Ogi et al., 2021), and are therefore highly relevant to measuring their social anhedonia as well. For example, the shoaling test examines group cohesion (*e.g.*, shoal area and an average inter-fish distance) (Miller and Gerlai, 2007; M. O. Parker et al., 2013c; Robert Gerlai, 2014; Carreno Gutierrez et al., 2019), whereas the social preference test assesses the number of approaches and time spent near a conspecific (R. Gerlai et al., 2000; Norton et al., 2019). In contrast, exposure to acute and chronic stress decreases social interaction in adult zebrafish, manifested as shorter time near conspecifics in the social preference test and shorter average inter-fish distance in the shoaling test (Giacomini et al., 2016; K. A. Demin et al., 2020b).

Animal anhedonia is also commonly associated with decreased novelty-seeking behavior, such as novel object or novel environment exploration (Strekalova et al., 2004). In zebrafish, various protocols have been developed to assess their exploration of a novel object (May et al., 2016; Gaspary et al., 2018; Magyary, 2019) or novel environments (Godwin et al., 2012; A. M. Stewart et al., 2012), thereby providing a potential tool to assess fish anhedonia by measuring reduced novelty-seeking. Interestingly, exploration of an unfamiliar conspecific fish (Madeira and Oliveira, 2017; Ribeiro et al., 2020) may combine both types of appetitive (social preference and novelty-seeking) behaviors, whose inhibition may potentially reflect both aspects of anhedonia in zebrafish, and can conveniently be simultaneously assessed in one aquatic 'combined' test. Reduction in other appetitive behaviors, such as sexual interaction (Spence and Smith, 2006), palatable food consumption (B. Lau et al., 2006), preference for warm temperature (Rey et al., 2015), social status (Dahlbom et al., 2011), can all potentially reflect anhedonia-like states in zebrafish, therefore warranting further studies.

Various novel genetic models of zebrafish anhedonia can also be interesting to develop. For example, the *too few* zebrafish mutation reduces selective groups of dopaminergic and serotonergic neurons in the basal diencephalon, and generates normal food preference but no preference for morphine (B. Lau et al., 2006). In contrast, pretreatment with dopamine receptor antagonists abolishes morphine preference in the wild-type fish, suggesting that preference for natural reward and addictive drug in zebrafish can be dissociable by a single-gene mutation that alters subregions of brain monoamine neurotransmitter systems (B. Lau et al., 2006). As such, genetic models with impaired reward in zebrafish (e.g., similar to the *too few* mutation) can be developed with potential relevance to modeling anhedonia in this species.

Pharmacological models of anhedonia: from rodents to zebrafish?

Multiple pharmacological manipulations are used to treat depression pathogenesis (Table 3), and may therefore alleviate clinical anhedonia as part of their therapeutic profile (Cao et al., 2019). Paralleling clinical data, antidepressants fluoxetine and imipramine, as well

as typical and atypical antipsychotic drugs, reverse stress-induced neurochemical alterations and reduce rodent anhedonia (Noda et al., 2000; Vardigan et al., 2010; Chatterjee et al., 2012; Bessa et al., 2013).

For instance, aripiprazole restores rodent motivation to receive reward impaired by UCS (S. Scheggi et al., 2018b), olanzapine not only prevents, but also reduces rodent stress-evoked anhedonia, whereas haloperidol prevents anhedonia when administered before (but not after) stress (Orsetti et al., 2006). In zebrafish, several anxiolytic, antipsychotic and antidepressant drugs have also been tested following acute and chronic stress exposure (Konstantin A. Demin et al., 2020a). Zebrafish chronically treated with fluoxetine, bromazepam or nortriptyline display blunted behavioral and endocrine (e.g., whole-body cortisol levels) responses to UCS (Marcon et al., 2016; C. Song et al., 2018a). However, putative more specific roles of anxiolytic, antipsychotic and antidepressant drugs in zebrafish anhedonia-like phenotypes merits further scrutiny.

Promises, problems and limitations of zebrafish models of anhedonia

As there is an urgent need to develop novel translational animal models of anhedonia, using animal models to understand human diseases must consider widening the spectrum of model organisms used. Indeed, the greater number of species studied increases the behavioral repertoire that can be evaluated and may more fully mimic the observed behaviors in the human syndromes or symptoms of these disorders. In line with this, as already mentioned, zebrafish possess a generally similar brain architectonics to that of mammals (Wullimann et al., 1996), including the reward circuits and shared neurotransmitters and hormones (P Panula et al., 2010) traditionally associated with anhedonia states. Moreover, zebrafish models have also been developed for several common CNS disorders with frequent anhedonic phenotypes, including depression (Fonseka et al., 2016; de Abreu et al., 2018) and schizophrenia, as well as for chronic stress (Konstantin A. Demin et al., 2019; Gawel et al., 2019; Campbell and Granato,

2020; Costa et al., 2021). In addition, zebrafish also offer several clear advantages to study anhedonia and its therapy. For example, these fish have a high degree (~70%) of genetic homology to humans (Howe et al., 2013), including a large number of orthologous genes of the serotoninergic, dopaminergic, opioidergic, GABA-ergic systems (Kim et al., 2004; P. Panula et al., 2006; Lillesaar, 2011; Konstantin A. Demin et al., 2018) relevant to anhedonia. The availability of modern gene-editing tools for zebrafish remarkably surpasses that of rodents (Kaili Liu et al., 2019; Sharma et al., 2021). As such, developing innovative genetic models of anhedonia in zebrafish may be an important, feasible and promising strategy of research in this field.

Likewise, adult and especially larval zebrafish are particularly suitable for medium- and high-throughput CNS drug screening (Adam Michael Stewart et al., 2015; Khan et al., 2017). As such, the possibility of testing multiple antidepressants in zebrafish models enables not only targeting anhedonia-like phenotypes as part of their broader antidepressant action, but also may help identify anhedonia-specific CNS drugs, as well as, eventually, discover drugs that can differentially correct various subtypes of anhedonic behaviors. Zebrafish have also sophisticated behavioral responses easily assessed using automated video-tracking systems, increasing the efficiency and speed of time-intensive manual coding (Kalueff et al., 2013b), that may be helpful for extracting anhedonia-related phenotypes and foster an in-depth investigation of pharmacological correction of anhedonia-like phenotypes. Collectively, this supports zebrafish as a promising species to explore pathobiology of anhedonia.

Notably, as depression is often triggered by stress, and given high sensitivity of zebrafish to chronic stress, this aquatic species may be suitable not only for modeling depression-like states in general (Marcon et al., 2016; C. Song et al., 2018a), but anhedonia in particular, as a core symptom of depression. For example, paralleling low dopamine levels (suggested to cause anhedonia in mammals (Gorwood, 2008)), UCS evokes depression-like motor retardation and reduced brain serotonin and dopamine levels in zebrafish (M. Nguyen et

al., 2014b; Zakaria et al., 2021). Likewise, chronic treatment of adult zebrafish with an antidepressant fluoxetine normalizes anxiety- and motor retardation-like behavioral deficits, as well as cortisol and pro-inflammatory cytokines induced by UCS (C. Song et al., 2018a). However, the effects of UCS on zebrafish anhedonic-like phenotypes are unclear, and necessitate further studies. The role of other factors that induce or promote mental disorders like depression (e.g., psychological traumas associated with the loss of a family member) clinically can also be hypothetically used to develop models that induce stress-related (including socially-mediated) anhedonic-like phenotypes in zebrafish. If successful, such findings would further support zebrafish as a potentially promising candidate aquatic model organism to probe the link between chronic stress, depression- and anhedonia-like phenotypes.

Furthermore, the sickness behavior, induced by infections and mediated by pro-inflammatory cytokines (Maier and Watkins, 1998), is another pathological syndrome relevant to depression. Indeed, activated brain cytokines are associated with depression pathogenesis (Dantzer, 2001), which, in turn, shares considerable phenomenological similarities with sickness behavior (Dantzer, 2009; Maes et al., 2012). For example, they both share motor retardation, anorexia, weight loss, anhedonia, somatic (fatigue, hyperalgesia and malaise), anxiety and neurocognitive deficits (Maes et al., 2012). Similar to anhedonia, humans also exhibit decreased appetite during both illness and depression (Plata-Salamán, 1996; Simmons et al., 2016). Likewise, rodent infection and inflammation are commonly accompanied by reduced food intake (Bernstein et al., 1985; McHugh et al., 1993). For example, mimicking food anhedonia, the acute administration of endotoxin lipopolysaccharide (LPS) reduces self-administration of sucrose pellets in rats (De La Garza et al., 2004). Similarly, rat sepsis model with polymicrobial abdominal infection evokes sickness behavior and fever, as well as anhedonia-like low activity/ energy (lethargy), SP and body weight loss (Pereira de Souza Goldim et al., 2020).

Strikingly paralleling rodent findings, sickness behavior can be induced in adult zebrafish by formalin-inactivated bacteria, reducing fish locomotor activity (motor retardation), social preference (social anhedonia) and exploration of a novel object (reduced novelty-seeking behavior), in addition to up-regulating brain expression of pro-inflammatory cytokines (e.g., interleukins IL-1β, IL-6, and tumor necrosis factor, TNF-α) (Kirsten et al., 2018). In line with this, pharmacological therapies can revert some of these deficits in various animal models (Yirmiya, 1996; Yirmiya et al., 2001; Sammut et al., 2002; Merali et al., 2003). For example, chronic treatment with a tricyclic antidepressant, imipramine, or fluoxetine abolishes reduced rat SP produced by acute LPS (Yirmiya, 1996; Yirmiya et al., 2001), interferon (IFN)-α (Sammut et al., 2002) or IL-1β (Merali et al., 2003).

Anhedonia can be conceptually modeled in animals as reduced reward in multiple ways, from targeting simpler cognitions (e.g., reward valuation assessed by delay or effort) and reward responsiveness (e.g., anticipation, initial response to it, its satiation), to recapitulating more complex cognitive processes, such as learning from the reward (e.g., by assessing probabilistic and reinforcement learning or reward prediction errors) (Simona Scheggi et al., 2018a). Thus, zebrafish models based on reduced reward anticipation or impaired reinforcement learning may also be a promising avenue of translational research modeling anhedonia across taxa. At the same time, zebrafish models also have some clear limitations in terms of their translatability into human anhedonia, especially given certain differences from mammals in brain neuroanatomy (Matthew O. Parker et al., 2013b). For example, cortex plays an important role in mammalian reward circuits (Haber and Knutson, 2010), in addition to the nucleus accumbens, ventral pallidum and orbitofrontal cortex (OFC) (Der-Avakian and Markou, 2012). The OFC and ventral striatum receive inputs from sensory cortices and

calculate the reward values, while the OFC projects reward value information to the rostral anterior cingulate cortex projecting to the prefrontal cortex. The latter has bidirectional connections with multiple areas, including the dorsal raphe, ventral tegmental area, and locus coeruleus, which play an important role in adaptive responses to reward and decision-making (Der-Avakian and Markou, 2012). However, since zebrafish lack cortex (Matthew O. Parker et al., 2013b), they may not be appropriate models to study various aspects of cortically driven modulation of anhedonia.

Moreover, small body size (Lakstygal et al., 2018) of zebrafish not only complicates their video-recording, but also the development of operant and/or touchscreen-based assays for studying CPP deficits that are relevant to modeling anhedonia. The small size of zebrafish brain also complicates the development of intracranial self-stimulation protocols, commonly used to study anhedonia in rodents (Simona Scheggi et al., 2018a), as well as real-time analyses of neurochemical markers in specific brain regions (L. J. Jones et al., 2015).

Inadequate maternal behavior is an important factor in triggering anhedonia in both humans (Widom et al., 2007) and rodents (Molet et al., 2016). For example, FSL rats display reduced motivation to lick, contact and care for pups (Lavi-Avnon et al., 2005), which may underpin their anhedonia-like behavior as adults (Lavi-Avnon et al., 2005). However, maternal behavior is absent in some fishes, including zebrafish (Perrone Jr and Zaret, 1979), and therefore cannot be used to develop translationally relevant models of anhedonia based on maternal influences. Likewise, social defeat is a common model to induce depression-like anhedonia phenotypes in rodents (Hollis and Kabbaj, 2014; Riga et al., 2015), but is less straight-forward in zebrafish., whose repeated social defeat (e.g., by social subordination for 6 days) reduces the motivation to fight, likely representing a more specific and distinct, social subtype of anhedonia (Nakajo et al., 2020).

Although anhedonia is commonly found in patients with chronic pain (Garland et al., 2020), and zebrafish present robust models to study pain (Costa et al., 2021), their potential to evoke anhedonia is unclear (Table 4). In addition, robust sex differences are also reported in anhedonia, as men score higher on physical anhedonia and social anhedonia scales (Miettunen and Jääskeläinen, 2010) and display greater anhedonic depression than women (Langvik et al., 2016). Likewise, female mice display longer latency to eat in the novelty-suppressed feeding test (Paden et al., 2020). Although robust sex differences are also noted for zebrafish behaviors (e.g., UCS increases aggression in males, but not in females (Rambo et al., 2017)), the role of sex in zebrafish anhedonia-like phenotypes remains unclear (Table 4), and warrants further studies.

Modeling zebrafish anhedonia also meets some translational challenges. For example, it is difficult to measure in fish several key clinical symptoms of anhedonia, such as negative feelings, and reduced emotional verbal or nonverbal expressions. In addition, anhedonia is a highly heterogeneous phenotype, and in depressed patients it may differ from that in schizophrenic patients (Culig and Belzung, 2016). For example, the latter may be characterized by a disorganization, rather than a deficiency, in reward processing and cognitive function, including inappropriate energy expenditure and focus on irrelevant cues. In contrast, depressed patients display deficits in anticipatory pleasure, development of reward associations, and integration of information from past experience (Lambert et al., 2018). Thus, the possibility to distinguish between different types of experimental anhedonia in animals, including both rodents and zebrafish, is yet to be established. Likewise, animal models cannot assess some other anhedonia-related feelings (e.g., sadness, guilt or suicidal thoughts), as such symptoms are limited to humans (Nestler and Hyman, 2010). Thus, modeling some subtypes of anhedonia (e.g., sadness-related anhedonia) in animals may be problematic. Nevertheless, it is possible to

model some other related anhedonia-like phenotypes (e.g., pessimistic bias), as telomerase-deficient zebrafish display more negative judgements in response to ambiguous stimuli than wild-type zebrafish (Espigares et al., 2021). Some other important conceptual questions remain in regard to animal anhedonia models in general, including zebrafish anhedonia (Table 4). For example, is animals' behavior anhedonic-like because they are 'depressed', or, alternatively, does depression emerge first and then induce anhedonia-like states? These two possibilities must clearly be considered when planning experimental protocols to study complex dynamics of anhedonia pathogenesis in zebrafish and other species.

Despite these challenges, mounting evidence summarized here indicates several key characteristics – the presence of selected anhedonia-related behaviors in zebrafish and the availability of sensitive behavioral tests capable of assessing these anhedonic phenotypes, that together with the growing number of experimental models evoking anhedonia-like states, support the zebrafish as a promising experimental model to probe the pathobiology of anhedonia. However, as many questions regarding anhedonia in zebrafish remain open (Table 4), further studies are needed to better understand the pathobiology of zebrafish anhedonia-like states, as well as to develop novel therapies to correct these phenotypes in zebrafish-based screens. Overall, all advantages of zebrafish models discussed here make this animal a valuable and unique species to study anhedonia pathobiology.

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

Figure 1. **Summary of anhedonic phenotypes in humans, rodents, and zebrafish (see Tables 1 and 2 for details).** Left panel shows that rodent anhedonia-like behavioral responses can be assessed by conditioned place (CPP) or sucrose preference (SP) tests (Cunningham et al., 2006; Simona Scheggi et al., 2018a). For example, male C57BL/6 mice exposed to chronic stress display reduced SP, a behavioral sign of anhedonia (Strekalova et al., 2004). Right panel illustrates zebrafish CPP models developed to measure reward-like phenotypes, hence reflecting their potential to assess anhedonia (Priya Mathur and Guo, 2010; P. Mathur et al., 2011; Hinz et al., 2013; Adam D. Collier et al., 2014; Daniela Braida et al., 2020). For example, zebrafish clearly prefer reward-associated CPP compartments (*e.g.*, paired with morphine, diazepam, fluoxetine, risperidone, and buspirone) (B. Y. Lau et al., 2011; Abreu et al., 2016), and also offer several other behavioral tests assessing social phenotypes (relevant to social anhedonia) (Pham et al., 2012; Asahi Ogi et al., 2021), as well as novelty-seeking behavior (novel object or environment exploration (Strekalova et al., 2004)), reflecting decreased exploration of novelty. Finally, like humans, zebrafish present generally similar, conserved brain structures and circuits (Matthew O. Parker et al., 2013b), including serotonergic and dopaminergic systems strongly involved in anhedonia pathogenesis.
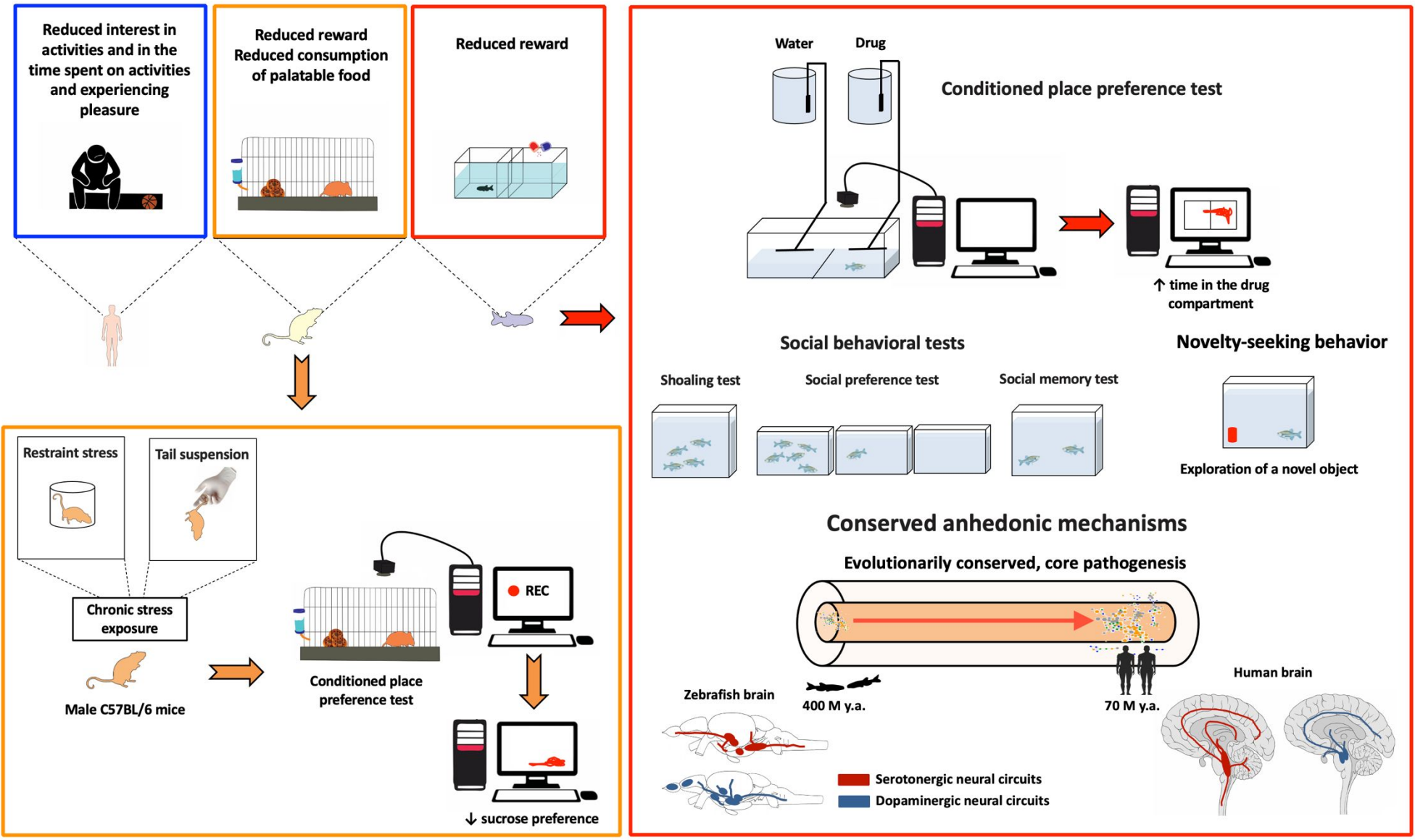
Table 1. Summary of key anhedonic phenotypes in humans, rodents and zebrafish

Humans	Rodents	Zebrafish
Reduced interest in activities and in the time spent on activities and experiencing pleasure	Reduced reward behavior (e.g., in conditioned place preference (CPP) tests)	Reduced reward behavior (e.g., in CPP, hypophagia)
Loss of appetite	Reduced consumption of palatable food	Loss of food preference in the CPP
Social withdrawal	Social deficits (reduced social interaction or preference, low social hierarchy)	Social deficits (reduced social interaction, social preference and shoaling behavior, low social hierarchy)
Lethargy, hypoactivity (motor retardation), loss of energy	Hypoactivity (motor retardation)	Hypoactivity (motor retardation)
Loss of libido	Reduced sexual behavior	Reduced sexual behavior
Reduced emotional abilities (e.g., having less verbal or nonverbal expressions)		
Reduced ability to learn from reward	Reduced ability to learn from reward	Reduced ability to learn from reward
Sensitivity of anhedonic phenotypes to antidepressants	Sensitivity of anhedonia-like phenotypes to antidepressants	Sensitivity of anhedonia-like phenotypes to antidepressants

Table 2. Selected tests to study anhedonia in humans, rodents and zebrafish (see

(Thomsen, 2015) for details).

Anhedonia-like phenotypes	Humans	Rodents	Zebrafish
Impaired ability to learn about reward	Conditioned preference to a methamphetamine-associated contextual cue (Mayo et al., 2013; Mayo and de Wit, 2015), Pavlovian-to-instrumental transfer task (Garofalo et al., 2020)	Conditioned place preference (CPP) (Tzschentke, 1998, 2007) and avoidance (CPA)(Zang et al., 2020)	CPP (Wong et al., 2014) and CPA(Wong et al., 2014)
Impaired ability to pursue reward (*e.g.*, food or sex)	Incentive key press/force grip (Aharon et al., 2001; Parsons et al., 2011), attentional blink (Field et al., 2009; Tibboel et al., 2010), effort expenditure for rewards task (EEfRT)(Treadway et al., 2009)	Effort to obtain reward (K. C. Berridge and Valenstein, 1991; Pecina et al., 2003), palatable food intake (Salamone et al., 1994; Salamone et al., 2007), Pavlovian instrumental transfer (Wyvell and Berridge, 2000, 2001), female urine sniffing test (Malkesman et al., 2010)	-
Impaired ability to experience pleasure	Self-reports (Jarratt-Barnham et al., 2020; El Sayed et al., 2021), facial expressions (Bylsma et al., 2008), rectal pressure variability(Georgiadis et al., 2006)	Facial "liking" reactions and "disliking" reactions (Grill and Norgren, 1978b, a)	-
General anhedonia	-	Social interaction test (File and Hyde, 1978)	Social preference (A. Ogi et al., 2020)
	-	Sucrose preference (SP) test (M. Y. Liu et al., 2018)	Food size preference (Onal and Langdon, 2016)
	Self-administration (J. D. Jones and Comer, 2013)	Intracranial self-stimulation (Redgrave and Dean, 1981), self-administration (Figlewicz et al., 2011; Huyts et al., 2019)	Self-administration (Bosse and Peterson, 2017)

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Table 3. Selected clinically relevant drugs to treat affective anhedonia-related phenotypes in

humans, rodents and zebrafish

Substance	Human effects	Rodent effects	Zebrafish effects	References
Agomelatine	Reduces severity of anhedonia, depression and anxiety	Reduces anxiety- depression- like behaviors		(Gargoloff et al., 2016; Lapmanee et al., 2017)
Amantadine	Antidepressant effect in bipolar depression	Antidepressant-like effects in the forced swim test, chronic mild stress paradigm, and reserpine test		(Raupp-Barcaro et al., 2018; Krzystanek and Pałasz, 2020)
Bupropion	Antidepressant effect with robust improvement of self-reported anhedonia.	Causes social anhedonia		(Tomarken et al., 2004; Lipina et al., 2013)
Flibanserin	Improves libido in depressed women	Increased sucrose intake in stressed mice		(D'Aquila et al., 1997; Kennedy, 2010)
Fluoxetine	Improves at endpoint on the Montgomery-Asberg Depression Rating Scale (include anhedonia)	Increased palatable sweet solution intake in stressed mice	Chronic administration promotes exploration and lowers whole-body cortisol levels	(Muscat et al., 1992; Corrigan et al., 2000; Egan et al., 2009; Cachat et al., 2010)
Ketamine	Reduced anhedonia in depressed patients	Increased sucrose preference in rats exposed to 21-day unpredictable chronic stress		(Nanxin Li et al., 2011; Lally et al., 2014; Lally et al., 2015; Ballard et al., 2017)
Maprotiline	Antidepressant effects	Antidepressant effects, reversed stress-induced anhedonia		(S. W. Li and Yan, 1989; Muscat et al., 1992)
Moclobemide	Antidepressant effect, reduced social phobia	Reversed stress-induced anhedonia		(Moreau et al., 1993; Bonnet, 2003)
Pramipexole	Antidepressant effect	Reversed stress-induced anhedonia		(Willner et al., 1994; Corrigan et al., 2000)
Sertraline	Antidepressant effect, reduced anhedonia in patients with major depression	Antidepressant effects	Reversed reserpine-induced depression and cognitive deficits	(Boyer et al., 2000; Ulloa et al., 2010; Zhang et al., 2018)

Table 4. Selected open questions related to zebrafish anhedonia models.

Questions

- Are there individual, strain and sex differences in anhedonic responses in zebrafish?
- What are reliable physiological (non-behavioral) biomarkers of anhedonia in mammals? Are these biomarkers shared between mammals and zebrafish?
- Do anhedonia-like and sickness behavior-like phenotypes overlap in zebrafish models?
- Do olfactory deficits (*e.g.*, long-term anosmia) translate into zebrafish anhedonia?
- Is there a clear hierarchy of motivations in animals and humans, and how it relates to anhedonia in zebrafish?
- Since depressive disorders are a heterogeneous group, where is anhedonia in these clusters of endophenotypes?
- Are there differences across age in zebrafish anhedonic response? Can anhedonia-like phenotypes be measured in zebrafish larvae?
- Can specific gene mutations influence anhedonia-like behaviors in zebrafish?
- How gene expression correlate with anhedonic responses in zebrafish models?
- Can zebrafish anhedonia, if it exists, be epigenetically regulated?
- What are specific neural circuits (e.g., involving habenula) implicated in zebrafish anhedonia-like states?
- Can zebrafish models based on light or temperature be developed to assess zebrafish anhedonia?
- Can zebrafish chronic pain models induce anhedonia-like phenotypes?
- Can there be fully automated models and tests to assess zebrafish anhedonia?
- Do zebrafish temperamental traits (e.g., boldness/shyness, pessimistic/optimistic bias) correlate with anhedonia-like states?
- How can anhedonia be separated from fatigue in animal models, including zebrafish?
- Can we model complex cognitive phenomena, such as motivation loss and avolition, in relation to zebrafish anhedonia?
- Can different subtypes of clinical anhedonia be modeled in zebrafish? Are there state vs. trait anhedonia models in zebrafish?
- Can zebrafish models be developed for both specific and generalized anhedonia states?
- Can zebrafish models of anhedonia overlap with (and be relevant to) some other related CNS states, such as cognitive inflexibility?
- What is the complex dynamic relationship between depression and anhedonia? For example, is animals' behavior in some models *anhedonic-like* because they are 'depressed', or, alternatively, can depression emerge first, and then induce secondary anhedonia?

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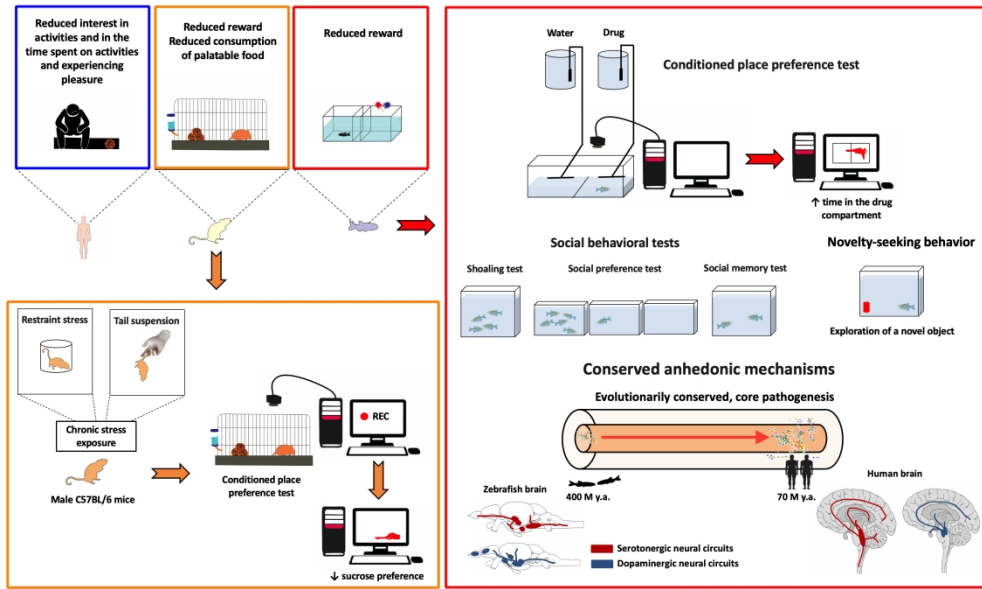
Figure 1

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