Developing Zebrafish Depression-Related Models

Julian Pittman and Angelo Piato

Abstract Animal models of disease are ultimately only as strong as the clinical phenotype(s) upon which they are based. Many obstacles impede our ability to design animal models of complex mental illnesses, such as depression. An animal model that attempts to re-create any disease strives to maximize construct, face, and predictive validities. Strategies to model depression in representative animals have largely focused on one or more symptoms of depression, which have left many knowledge gaps open. In approaching these knowledge gaps, there are three primary areas that we feel need to be focused on: development of translational animal models, identification of genetic determinants, and discovery of novel targets/biomarkers of depression. Here, we discuss how zebrafish may be utilized in the modeling and analysis of the mechanisms of depression. Furthermore, this chapter also provides a detailed description of the behavioral responses and makes recommendations for further development of these methods, and how they may be employed in forward genetic screening for mutations involved in depression-related phenotypes.

Keywords Depression • Animal model development • Behavioral tests • Endophenotypes • Pharmacological analysis

1 Introduction

To translate basic science lessons learned from animal models of depression to clinical acumen, animal models of depression must be considered side-by-side with human presentation of symptoms of illness. Modeling human depression (see further) in animals poses unique challenges given contributions from higher-order functions such as

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emotions and cognitions to symptom presentations that are difficult, if not impossible to pinpoint and study in animals. The foundation of research into the mechanisms of depression must involve the development of novel behavioral paradigms, as they allow the quantification of functional changes in the brain induced by mutations or drugs, and will facilitate the discovery of underlying mechanisms and drug targets.

Depression is a common, serious and debilitating brain disorder [1]. Numerous studies have examined the biological mechanisms of depression, and a considerable amount of effort has been invested in the development of pharmacological treatments [2–9]. For preclinical research, most of these studies have used rodents. Since a large amount of data has been accumulated on rodent species, it may seem logical to think that building upon this well-laid foundation is the only way to proceed. The abandonment of rodent research is certainly not likely or recommended; however, utilization of another vertebrate, zebrafish, appears to be a fruitful direction to pursue namely because they are robust, small, reproduce quickly and possess evolutionarily conserved traits.

Zebrafish are showing promise as a model organism for experimental studies of affective disorders [5, 10, 11]. This species is demonstrating the potential to be an "exceptional" animal for investigating experimental, genetic, and pharmacological models of neurobehavioral disorders, such as depression [5, 8, 12–18]. As a result of the past three decades of intensive investigation with zebrafish, this species has become geneticists' favorite model organisms [16]. Zebrafish models strike an optimal balance between system complexity and practical simplicity, possessing brain anatomy, physiology, and genome very similar to those of other vertebrates including mammals [19–25]. Furthermore, they are small, easy and cheap to maintain in the laboratory, and are highly amenable to high-throughput screening (e.g., forward genetic or drug screens). The latter is particularly noteworthy for the purposes of unraveling the genetic, and in general the biological, mechanisms of complex brain functions and the disorders of these functions. High-throughput screens may have the ability to identify a significant proportion of the potentially large number of molecular players involved in these functions [17, 26].

2 Pathogenesis of Depression and Model development

Depression remains a common disorder that affects approximately 15 million Americans, despite the increasing knowledge on its pathophysiology and treatment [19]. One of the obstacles is the lack of validated diagnostic tests based on biological markers, which would allow us to predict treatment response in depressed patients. Also, biomarkers that correlate to treatment response to antidepressants or psychotherapy have not been identified so far. While imbalances in neurotransmitter levels are certainly involved in the pathophysiology of depression, no single neurotransmitter system is considered to be exclusively responsible. This is expected considering the range of symptoms included in the depressive syndrome: depressed mood, disinterest in usual activities, inability to feel pleasure, attention deficits, sleep disturbances, appetite alterations, and suicidal ideation. A novel conceptual approach is to consider depression as a systems-level 'spectrum' disorder that

concerns several critical brain regions and connecting pathways. In order to enable the development of scientifically-based rationales for innovative treatments, a comprehensive understanding of the neurobiology of depression and its genetic and environmental underpinnings is required.

The etiology of depression is currently viewed as a result of gene-environment interactions that ultimately impact the three major monoamines—serotonin (5-hydroxytryptamine, 5HT), norepinephrine (NE), and dopamine (DA). Recently developed tools in molecular biology and brain imaging have provided further evidence for the involvement of these neurotransmitter systems. Contrary to earlier views [21], recent observations now support a preeminent role for central dopaminergic circuits [27], which could explain the now well-reported suboptimal response to selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs).

Animal models cannot replicate the symptoms of depression in a complete manner, since core symptoms of the disorder such as depressed mood, low self-esteem, or suicidality are not possible to access in non-humans [25, 26, 28]. On the other hand, there are depression endophenotypes that can be individually reproduced and evaluated in animals [29]. Ideally, an animal model should represent a means to understand the molecular, genetic, and epigenetic factors involved in the etiology of depression. Animal models also afford insight into the pathology of depression by allowing us to examine underlying molecular alterations and the causal relationship between genetic or environmental factors, which are indispensable to develop novel therapies with greater efficacy. The attempt to model a single symptom or endophenotype of a disorder, rather than to recapitulate its full phenotypic expression, is especially relevant for medical disorders of unclear pathophysiology or genetic etiology, such as depression. For behavioral measures to be used as novel models they should meet reliability, predictive, construct and face validity criteria as much as possible [23, 30].

3 Novel vs. Familiar, Open Field, Social Isolation Tests

Various methods have already been developed to induce and study depression-related behaviors. Novelty is classically recognized as an anxiety-inducing factor in several species, including humans. For instance, in the “open field test” rodents [31, 32] and other animals, including fish [22, 33], are exposed to an unfamiliar (thus potentially threatening) environment. The response to this novel environment is thought to be the resultant of two opposing and conflicting tendencies: exploration, an active response associated with the natural drive to explore unfamiliar places and objects, and anxiety, a passive response associated with harm-avoidance Both behaviors are considered adaptive, as exploratory activity may reveal food resources, mates and escape routes, while passive anxiety-induced responses (immobility/freezing) may reduce predation risk [32]. This interpretation may seem speculative, but quantitative genetic studies point towards ambidirectional selection forces as the basis for open field behavior. Thus, natural selection in rodents favored individuals that displayed intermediate behaviors (not too active but not too passive either) [32], an observation that extends to

other vertebrates including fish [34]. This represents a particularly valuable application for measuring depressive behavior in zebrafish and for identifying new genetic lines.

The evolutionary past of zebrafish is likely similar to that of mice and rats considering that zebrafish has also been under ambidirectional selection with regard to behavioral responses induced by novelty. Therefore, when exposed to a novel environment, zebrafish are expected to display moderate levels of anxiety-like behavior. Importantly, behavioral experimentation generally includes animal handling by humans, which also induces some level of anxiety. Analysis of novelty-induced anxiety responses in zebrafish [35], demonstrate initially low levels of exploratory activity that progressively increase across time. A typical "diving" response is observed, i.e., increased amount of time spent on the bottom of the test tank, which slowly decreases as the fish habituates to the novel environment [35] (see [22] for similar findings). Nicotine was shown to have anxiolytic properties as this drug reduced fear responses induced by novelty [35].

Decreased serotonergic activity is associated with depression and may be experimentally induced by social isolation [36]. Specifically, rodents display hyperactive and aggressive behavior following long-term social isolation, and anti-depressant treatment is able to block these consequences [37]. Such isolation paradigms based on serotonin deficits are used as experimental depression models in rodents [25], and may be similarly employed with zebrafish.

4 Stress Models

Several protocols of unpredictable chronic stress (UCS) were reported to induce depression-like behavior in rodents [38–40]. These UCS models, however, are expensive, time-consuming, long lasting (at least 4 weeks), and require a large physical infrastructure, besides presenting problems of reproducibility among laboratories [39, 41].

Although other labs [42, 43] investigated some aspects of stress in zebrafish, ref. [44] was the first report to describe an experimental protocol to study the effects of UCS in zebrafish. Compared to the most often used rodent protocols, a number of advantages can be highlighted, such as low cost, ease of maintenance and manipulation without the need for complex physical structure. In addition, while UCS protocols are usually conducted over at least 4 weeks in rodents [39, 45], zebrafish stressed during 7 or 14 days already showed behavioral, physiological and cellular responses consistent with those observed in rodents and chronically stressed humans [44]. The stress protocol induced anxiety, cognitive impairment and neuroendocrine dysfunction, as measured by increased cortisol and CRF levels and decreased GR expression. These results suggest that this model has adequate construct validity.

Subsequently, Chakravarty et al. [46] exposed zebrafish to a similar stress model for 15 days. This protocol induced anxiety-like behavior and decreased neurogenesis. The molecular markers corticotropin-releasing factor, calcineurin and phosphocyclic AMP were altered. Moreover, using proteomics analyses, 18 proteins were found to be modified in stressed-zebrafish, four of them (PHB2, SLC25A5, VDAC3 and IDH2) related with mitochondrial viability.

Another study [47] used a milder UCS protocol to study the effects of daytime and nighttime stress on inhibitory avoidance learning, cortisol levels and gene expression in Tuebingen zebrafish strain. Fish submitted to UCS displayed weaker inhibitory avoidance learning compared to the control group. Regarding cortisol, while fish submitted to 7 nights of UCS had higher levels of cortisol, no difference was observed after 7 or 14 days of UCS. Important changes in bdnf, grα, grβ, grβ/grα ratio, and mr genes were also observed after the 7-night UCS protocol.

In [48], the effects of a modified UCS protocol on molecular and physiologic parameters related to stress response were assessed. Zebrafish submitted to UCS protocol showed increase in cortisol levels and pro-opiomelanocortin, glucocorticoid and mineralocorticoid receptors, prolactin, brain-derived neurotrophic factor, hypocretin/orexin, and c-fos expression.

A recent study [49] also evaluated the effects of UCS on purinergic system in zebrafish. UCS induced decrease in ecto-ADA (adenosine deaminase) and increases in adenosine levels in zebrafish brain, without affect any ADA gene (*ada1*, *ada2.1*, *ada2.2*, *adaL*, and *adaasi*) expression using quantitative reverse transcription. The authors suggested that this increase in adenosine levels could help zebrafish to achieve homeostasis during UCS. The UCS model in zebrafish remains to be more fully pharmacologically validated, since its predictive validity was not assessed thus far. Given the rich behavioral repertoire and the complex social interactions of individuals in a group, this model may contribute to a better understanding of the effects of drugs modulating the stress axis (Table 1, Fig. 1).

Table 1 Main results of depression-related models in zebrafish

	Model	Main results	References
Genetic	Mutant gr^{s357}	↑ HPA axis	[50]
		Blunted suppression of cortisol by dexamethasone	
		↓ Spontaneous activity	[51]
Stress	Chronic stress	↑ Time in the tank bottom	[44]
		↓ GR expression	
		Impaired memory	
		↑ Cortisol and CRF expression	
		↑ Time in the tank bottom	[46]
		↓ Neurogenesis	
		Mitochondrial toxicity	
		↑ Cortisol	[47]
		Altered BDNF, grα, grβ, grβ/grα ratio, and mr genes	
		Impaired memory	
		↑ Cortisol levels	[48]
		↑ POMC, GR, MR, prolactin, BDNF, hypocretin/orexin, and c-fos expression	
		↑ Adenosine	[49]
Drug	Reserpine	Impaired locomotion	[52]

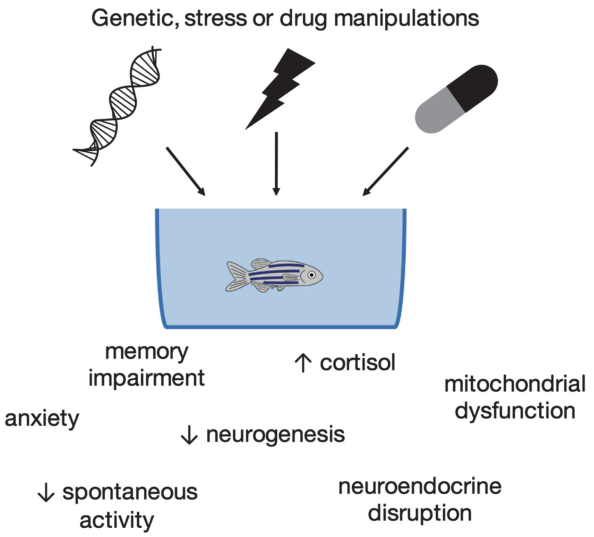

Fig. 1 Effects of different manipulations on behavioral, physiological and molecular parameters relevant to depression in zebrafish

5 Pharmacological Models for Depression-Like Responses

The motivation for the continued search for improved drugs to treat depression is not only to improve the quality of life of those suffering from it, but also to aid in our understanding of how depression develops, and what biological mechanisms may underlie this disorder cluster. Another reason is that the currently available, however numerous, drugs are often not efficacious or do not work for all patients. One way zebrafish may be beneficial for such research is by speeding up the discovery of the biological mechanisms responsible for the symptoms of depression. This may be achieved using, for example, forward genetic screens that identify mutations leading to the isolation of underlying genes. Another completely different approach has been to search for compounds, or "small molecules", which may alter expression-like symptoms. It is thus important to consider what is known about the psychopharmacological properties of zebrafish in the context of depression. For example, can one consistently detect the efficacy of "gold standard" drugs for depression using zebrafish? That is to say, does the zebrafish model have predictive validity? Predictive validity is an important question for the use of novel model organisms. The principal theme with regard to the translational relevance of laboratory model organisms concerns the notion "evolutionary homology", i.e., conservation of biological function across previously utilized species (e.g., rodents), the novel laboratory species (e.g., zebrafish), and humans.

Many different pharmacological approaches can be employed to model depression [53]. An example is the administration of psychostimulants, such as amphetamine, which leads to hyperactivity and may be reversed by the administration of anti-manic treatments, such as valproate. Additionally, repeated administration of

psychostimulants induces a process of behavioral sensitization and may be used to model bipolar disorder [24]. Considering that repeated exposure to cocaine can lead to "cycling" in many neurochemical and physiological systems [54], bipolar-like behavior could be replicated in zebrafish, for instance, by combining cocaine with antipsychotic drugs. Another possibility is the induction of depressive-like behavior due to withdrawal of an anxiolytic agent, such as ethanol; this protocol requires chronic administration (minimum 3 weeks) of high doses of ethanol (1–3 %), and at least 7 days post-withdrawal before behavioral symptoms are manifest. The SSRI fluoxetine is able to reverse these depressive-like behaviors. In addition, quantitative changes in immunoreactive neurons are observed following this protocol of ethanol administration, mirroring many of the neurochemical findings of clinical depression [53].

There is a great number of studies reporting the effects of ethanol exposure across development in zebrafish. Findings comprise, for example, the strain-dependent effect of developmental alcohol exposure [55], the long-term effects of early embryonic ethanol exposure in adult animals [56], the development of adaptation (tolerance) and withdrawal symptoms following chronic ethanol exposure [34, 57, 58], and numerous alterations induced by acute ethanol administration [58]. Importantly, the behavioral effects of ethanol depend on concentration and administration regime, since lower doses of ethanol were shown to induce anxiolytic effects (see [58] and [22]), while prolonged exposure and withdrawal was associated with anxiogenic properties (see [57] and [22]). The behavioral effects induced by other drugs of abuse have also been documented for zebrafish. Cocaine, for example, has rewarding properties, and forward genetic screens have already been identified zebrafish mutants with altered cocaine reinforced place preference in [59]. Similarly to ethanol, also lead to anxiety/depression-related behaviors depending on drug concentration and administration schedules [60, 61].

Classical anti-anxiety drugs have been shown to exhibit an anxiolytic profile in zebrafish, such as fluromethylhistidine [62], benzodiazepines like diazepam, and the widely prescribed SSRI fluoxetine, that decreases bottom-dwelling, erratic movements, and whole-body cortisol levels [22], paralleling the responses observed in rodents [63]. On the other hand, acute administration of drugs known to induce anxiety in humans [64] and rodents [65], such as the benzodiazepine inverse agonist FG-7142 [61] and caffeine [22], led to increased anxiety responses in zebrafish, demonstrated by increased bottom-dwelling and erratic movements. Investigations of stress hormone levels in zebrafish have revealed numerous similarities when compared to the human stress response [5], strengthening the translational relevance of zebrafish as a model organism in depression research. The sight of a predator, for example, was shown to elevate cortisol levels in zebrafish [66]. It is important to note that cortisol is the primary stress hormone of the hypothalamic-pituitary-adrenal (HPA) axis in both human and zebrafish, but not in rodents, which use corticosterone instead. At the Society for Neuroscience meeting in San Diego (2010), Baier and his team demonstrated the generation of behavioral phenotypes resembling depression by disrupting the zebrafish stress response [67]. Another study [50] found a mutation in the glucocorticoid receptor gene in zebrafish that displayed depression-like

behaviors, suggesting that depression could be connected to an individual's capability to cope with stress. Furthermore, the SSRI fluoxetine (Prozac) ameliorated depression-like behaviors is animals carrying the mutation. Molecules targeting the glucocorticoid receptor and enhancing its activity instead of blocking it may lead to promising novel therapies for the treatment of depression.

Also, depression-like motor retardation and social withdrawal have been reported in adult zebrafish several days after exposure to reserpine [3]—a dopamine-depleting drug known to elicit depression-like responses in rodents and clinical depression in humans. However, with the use of all the above pharmacological treatments, one must exercise extreme care and ensure there is some ability to provide a dissection between anxiety and depression endpoints, especially given a high degree of comorbidity of anxiety with depression clinically. This may be achieved through careful selection of pharmacological agents and behavioral tests (much development is needed in this area), and confirmation of quantitative changes in neuronal circuits involved in depression.

6 Model Limitations and Future Directions of Research

A significant difficulty with using zebrafish in depression research is the fact that only recently the behavioral repertoire of this species has begun to be explored. Although the number of behavioral studies published on zebrafish is on the rise compared to classical laboratory species such as rat, mouse, or even the fruit fly, zebrafish behavioral research is still in its infancy [28]. With the lack of reliable behavioral tests and a thorough understanding of zebrafish behavioral features, the behavioral and neurochemical consequences of gene mutation or drug exposure will remain exceedingly difficult to study.

Given the complex mechanisms involved in the pathophysiology of depression, one may assume the necessity of identifying a considerable number of molecular players, i.e., genes and their protein products and the biochemical interactions between the proteins. A possibility to tackle this complexity may be, at least initially, to employ large scale screenings for mutations and drugs. This may result in the identification of potential targets and leads that may be followed up on by more targeted hypothesis-driven analyses. We are not, however, advocating large screening as the only fruitful approach. A large number of mechanisms is awaiting to be revealed, and "blind", i.e., unbiased, screening applications may facilitate their discovery. This is where zebrafish poses a major advantage over the classical laboratory organisms.

The development of novel behavioral endpoints and observational methodologies, such as automated video-tracking systems, is important to reinforce the utility of zebrafish as a model organism for depression research. The use of biomolecular markers, such as gene and protein expression, to parallel zebrafish physiology with behavioral data represents another critical research direction to pursue.

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