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Exploring the utility of zebrafish models for understanding neuropsychiatric disorders and advancement of drug discovery

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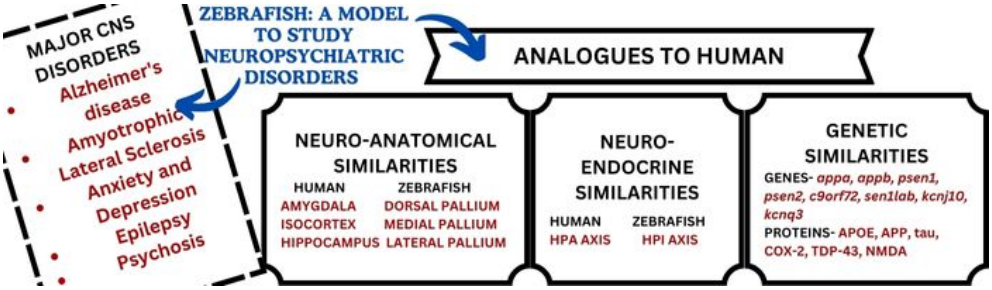
Review

ABSTRACT



Human neuropsychiatric disorders are modelled in zebrafish (*Danio rerio)* to facilitate advancements in drug discovery and for simulating complex neurological and psychiatric disorders. The zebrafish exhibits a variety of behaviors analogous to human psychiatric symptoms, such as social interaction, aggression, sleep patterns, learning, memory, and anxiety. The studies on their neuroendocrine system that mirrors the human Hypothalamic-Pituitary-Adrenal (HPA) axis, can provide insights into neurological illnesses. Here, we discuss selected examples of successful applications of zebrafish models for studying the underlying molecular and genetic mechanisms of neurodegenerative diseases, including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), anxiety, depression, epilepsy and psychosis. The research has greatly benefitted by using the zebrafish model to mimic the pathological conditions of these diseases for drug discovery. In this review, we summarize the zebrafish as a versatile and cost-effective model for exploring the genetic, molecular, and behavioral aspects of neuropsychiatric disorders and for related drug discovery studies. Therefore, research utilizing the zebrafish models can pave the way for significant findings to be translated into clinical therapies.

Keywords: Zebrafish; Neurological diseases; Neuropsychiatric disorders; Alzheimer's disease; Anxiety and Depression.

INTRODUCTION

The common and severe neuropsychiatric illnesses affect millions of people worldwide. Their causes are poorly understood and the treatment procedures remain inadequate.[1,2] Identifying genetic, environmental, and clinically relevant biomarkers, along with understanding the neurological causes of psychopathology, is crucial for developing effective therapies.[3,4] Despite the well-established use of laboratory rodents in studying human brain disorders, the high costs and limited effectiveness of these animals as experimental models constrain their applicability.[5] Zebrafish (*Danio rerio)* has emerged as a valuable and commonly available model organism for neuroscientific systematic studies.[6-9] This vertebrate model system allows in-depth investigation of the precise function of genes and the signalling pathways in the progression of neurodegeneration.[10] Both larvae and adults of the zebrafish are useful preclinical *in vivo* models for genetic modification in experimental therapeutics.[11-13]

Zebrafish offer numerous experimental advantages. First, zebrafish are very easy to maintain in the laboratory environment, simple to stimulate the essential conditions for the experiment and grow profitably. Second, their three to five months' short generation duration accounts for their rapid experimental procedure.[14] Third, external fertilization and embryonic growth patterns facilitate easy monitoring and experimental manipulation in zebrafish. Fourth, zebrafish offer the unique advantage of optically transparent eggs post-fertilization, enabling the easy visualization of individual genes with non-invasive imaging techniques, such as fluorescent labeling.[15-19] Finally, the zebrafish genome has been completely sequenced and shares approximately 82% similarity with genes associated with human diseases. This

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similarity spans gene sequences, functions, and other characteristics, highlighting their relevance to human health conditions.[20] The zebrafish are ideal for high-throughput screening of neuroactive compounds due to their small size, ease of breeding, and straightforward maintenance, which allow for efficient genetic manipulation and analysis.[21,22] Additionally, zebrafish brain atlases and gene expression data provide valuable tools for studying the neuroanatomy and genetics of brain regions associated with human neuropsychiatric disorders.[23-25]

This review highlights the growing importance of zebrafish as a model organism for studying neuropsychiatric disorders and advancing drug discovery. Here, we also discuss selected neuropsychiatric conditions, including Alzheimer's disease, Amyotrophic Lateral Sclerosis, anxiety and depression, epilepsy, and psychosis, emphasizing their underlying causes and potential drug development targets that can be explored using zebrafish.

CNS Architecture in Zebrafish and Humans

The zebrafish CNS is simpler including the encephalon with all major brain regions such as the forebrain, midbrain and hindbrain (Fig 1A and B). The olfactory nerve provides access to both the olfactory bulb and the dorsal and ventral regions of the zebrafish telencephalon. The diencephalon is situated posterior to the midbrain and is mostly enclosed in the optic tectum. The preglomerular region, hypothalamus, optic nerve, Torus lateralis, and habenula are among the diencephalon's externally clear structures. The cranial nerve roots, except the optic and olfactory nerves, are housed in the brain stem where the cerebellum covers the rostral side. The region encompasses the crista cerebellaris, unpaired facial lobe, and prominently paired vagal lobes at the end. The spinal cord (medulla spinalis) develops from the medulla oblongata (Fig 1). A range of imaging techniques can be utilized to observe CNS activity in zebrafish that provide crucial insights into the connection between brain function and both normal and abnormal behaviours.[26] The high-quality *in vivo* imaging and the manipulation of brain activity in live, behaving animals are enabled by the small size and superior visual clarity of larval zebrafish.[26]

Despite significant neuroanatomical differences between the central nervous systems (CNS) of mammals and teleost, zebrafish shares many fundamental structures and functions with mammals, making it a valuable model for research.[27] For instance, the dorsal, medial and lateral pallium of zebrafish resembles mammalian amygdale, isocortex and hippocampus respectively.[28-31] The primary neurotransmitter system including glutamatergic and inhibitory GABAergic neurotransmitters, along with muscarinic cholinergic receptors, show similarities between the zebrafish and human central nervous systems.[32,33] These similarities extend to the cellular level, where various types of neuroglial cells—such as astrocytes, microglia, oligodendrocytes, cerebellar Purkinje cells, Schwann cells, and motor neurons—are comparable to those found in humans.[34-39] Several studies have shown the analogy between the hypothalamus-pituitary-adrenal (HPA) axis in humans and the hypothalamus-pituitary-interrenal (HPI) axis in zebrafish is relevant regarding cortisol release, which binds to glucocorticoid receptors located in various body tissues.[40-42] These receptors help regulate multiple physiological and metabolic processes in response to stress. (Fig 2).

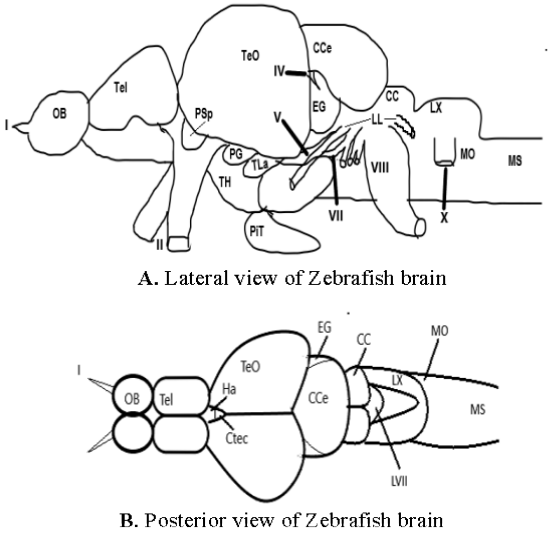

Figure 1. Lateral (A) and posterior (B) views of the zebrafish brain. CC: Crista Cerebellaris; CCe: Corpus Cerbelli; Ctec: Commissura tecti; OB: Olfactory bulb; Tel: Telencephalon; Psp: Parvocellular superficial pretectal nucleus; TeO: Tectum opticum; PG: Preglomerular area; TH: Tuberal hypothalamus; TLa :Torus lateralis; PiT: Pituitary; VIII: Octaval nerve; EG: Eminentia granularis; MO: Medulla oblongata; MS: Medulla spinalis; LX: Vagal lobe; Ha: Habenula; LVIII: Facial lobe; I: Olfactory nerve; II: Optic nerve; IV: Trochlear; V: Trigeminal nerve; VII: Facial nerve; X: Vagal nerve.

Fig 2 shows a diagram of the zebrafish neuromodulatory system, and the expression of thyroxine hydroxylase (TH) and secondary marker genes serves to identify the ventral diencephalon.[43-45] Telencephalon's pallium and subpallium of the telencephalon are separated by a dashed line that runs just over the area that expresses TH [46] (Fig 2). The habenula, subpallium, and ventral diencephalon are shown in green as having choline acetyl transferase-positive regions (Fig 2). The locus coeruleus's norepinephrine-containing cell bodies may be seen in the blue region. The blue lines in the illustration represent the forebrain projections of the zebrafish, extending to the subpallium, protectum, and ventral diencephalon (Fig 2).[44] In the ventral diencephalon, below the locus coeruleus region, pretectum, and pineal (between and above), the magenta region indicates the regions housing 5-HT (serotonin) cell bodies.[47]

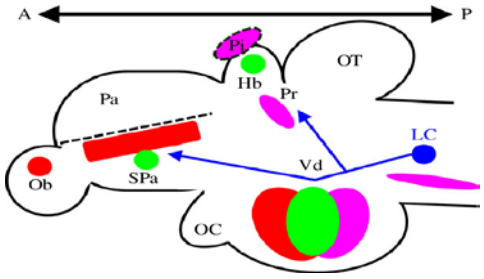

Figure 2: A sagittal image of the zebrafish brain. OC: Optic chiasm; LC: locus coeruleus; Ob: olfactory bulbs; Hb: habenula; OT: optic tectum; Pa: pallium; Pi: pineal body: Pr: pretectum; Spa: subpallium; Vd: ventral diencephalon.

Numerous invasive and non-invasive techniques can be used to harvest cortisol from zebrafish.[48-50] The neuroendocrine system of zebrafish can be readily explored through experimental, pharmacological, and genetic modifications. Several studies have established that changes in the neuroendocrine system cause several mental illnesses, like Alzheimer's disease, Anxiety, Sadness, and addiction.[51-58]

Zebrafish model for dominant CNS disorders

The major benefit of zebrafish for modelling CNS disorders is their adaptability to experimental, genetic, and therapeutic manipulations. Zebrafish show a very high degree of similarity to human CNS in behavioral phenotype, genetic factors, and pharmacological sensitivity. The following outlines how zebrafish models may be used to comprehend neuropsychiatric disorders, such as Alzheimer's disease, Amylotropic Lateral Sclerosis, anxiety and depression, epilepsy and psychosis:

Alzheimer's disease

The most typical neurodegenerative condition is Alzheimer's disease (AD). It is a neurological condition that worsens with time and is characterized by cognitive impairment, delusions, hallucinations, and behavioral and emotional disorders.[59] AD is a complex disease with no single cause, and several risk factors are responsible for its development and progression, which worsen with age. Most patients with AD are aged 65 years or older and typically have sporadic or late-onset AD (95%). Unusual genetic mutations that lead to the development of AD before the age of 65 are responsible for early-onset or familial Alzheimer's disease (<5% of all cases).[60] Sporadic AD has more complicated and poorly understood genetics. Studies indicate that the epsilon four allele of the apolipoprotein E (*apoE*) gene, located on chromosome 19, affects the onset of sporadic Alzheimer's disease (AD).[61] Orthologs of the *apoE* gene have been found in zebrafish.[62] The zebrafish model has shown specific features of the *apoE* gene involved in AD that have been challenging to identify in other animal models.[63,64]

Patients with Alzheimer's display numerous cognitive impairments in various areas (language, memory, visuospatial function, executive and reasoning). Patients with AD have a decreased ability to perform daily tasks and frequently struggle with psychiatric, mental, and personality issues. The primary pathological symptoms of AD are plaques and tangles (Fig 3).[65] Amyloid protein forms insoluble amyloid beta (Aβ) protein in senile plaques, which are extracellular aggregations. The aggregation of the Aβ peptide in the brain indeed triggers a cascade of events leading to AD. Typically, AD is characterized by aberrant processing of amyloid precursor protein (APP) by the β-secretase and the γ- secretase complex, resulting in the production of the amyloid β (Aβ) peptide, which precipitates amyloid beta into thick beta sheets and culminates in the development of senile plaques.[66] PSEN1 and PSEN2 code for presenilins, the catalytic components of the γ-secretase complex, which plays a role in the processing of amyloid precursor protein (APP).[67] Studies suggest the similarities between zebrafish preseninlin1(*psen1*), preseninlin2 (*psen2*), *appa*, and *appb* genes and *APP* genes and those of mammals (Table 1).[68] Elevated amyloid beta protein levels may promote cerebrovascular branching in the growing hindbrain of zebrafish.[69]

Neurofibrillary tangles (NFTs) are clusters of tau protein that have undergone abnormal hyperphosphorylation. Tau protein plays a crucial role in stabilizing microtubules and facilitating intracellular transport, serving as tracks that direct molecules and nutrients from the cell body to the ends of the axon and vice versa.[65] Various studies found that NFTs disrupt the normal transportation of important substances within axons, such as neurotrophic factors, mitochondria, and synaptic vesicles containing neurotransmitters.[65,70] This impairment negatively affects the survival and proper functioning of neurons. The human gene encoding tau protein is called the microtubule-associated *tau* gene. This gene also has zebrafish counterparts known as *mapta* and *maptb*.[71] There is an ongoing debate regarding the generation of NFTs and the accumulation of amyloid plaques in the progression of AD.

Hypoxia is another factor associated with AD.[68] Mitochondria may release free radicals under low oxygen conditions and these free radicals in turn cause oxidative stress in animals.[72,73] The sodium azide chemical and low water oxygen levels are commonly employed to induce hypoxic conditions in zebrafish.[74] Some AD related genes, such as *psen1*, *psen2*, *appa*, *appb*, and *bace1*, are upregulated under hypoxic circumstances in larval and adult zebrafish, similar to those in humans.[74]

The AD cholinergic system is also affected (which mediates memory and learning) [75] and showed reduced neurotransmitter binding sites of the nicotinic acetylcholine receptors and muscarinic acetylcholine receptors and reduced activity of acetylcholinesterase (AChE).[76,77] Flavonoids, a group of naturally occurring compounds found in plants, fruits, and vegetables, have gained attention in neuroscience and cognitive science fields owing to their potential neuroprotective and cognitive-enhancing effects. One of the mechanisms through which flavonoids exert their effects is by acting as AChE inhibitors.[78-80] Pretreatment with physostigmine, an AChE inhibitor, reduces the effects of scopolamine on zebrafish memory.[81] The fact that scopolamine can cause amnesia while allowing normal movement and locomotion is evidence that the neuronal cholinergic system is crucial for fish memory and learning.[82] The study also endorses the use of zebrafish as a drug discovery method and the development of medications that could help treat neurodegenerative ailments like AD. To better understand AD genesis, zebrafish are promising animal models.[82]

While there are many advantages to using zebrafish as a model system for AD research, there are also some disadvantages when applying this model to neuroscience studies. By putting the necessary chemicals into the water, it is simple to change a fish's pharmacological makeup. Although chemicals can be randomly absorbed by the skin and gills of fish due to exposure to whole-body aquatic habitats, the quantity of chemical compounds that enter the fish is higher than anticipated.[83] Another problem is that the characterization and role of Aβ peptides in zebrafish have not yet been fully elucidated. Additionally, further studies are required to determine whether zebrafish exhibit the same posttranslational processing of APP as humans.[84]

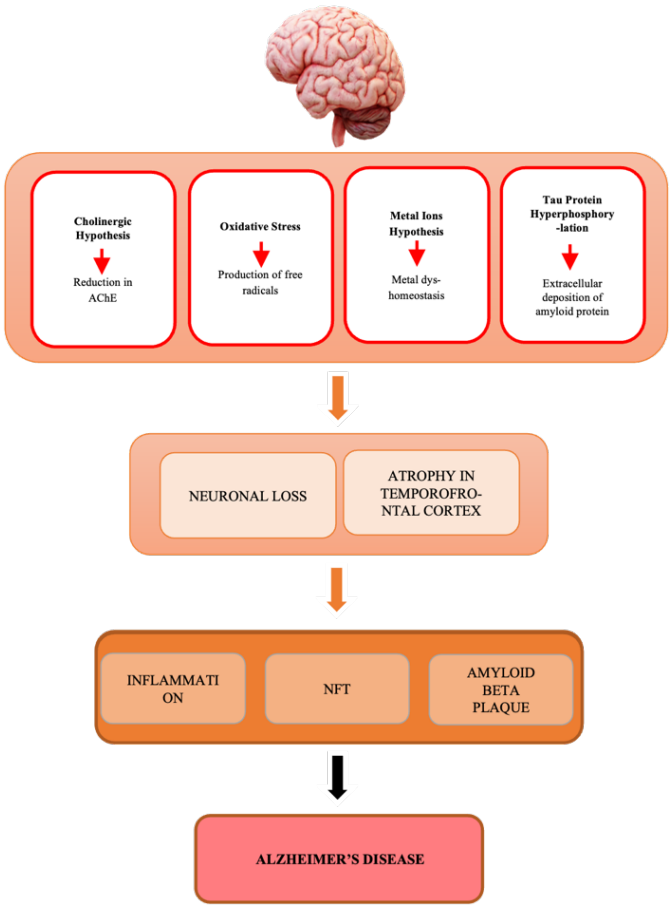

Figure 3: Pathophysiology of Alzheimer's Disease

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) eventually causes paralysis and death through the slow degeneration of motor neurons in the CNS. Zebrafish are a popular model for studying the normal and abnormal functioning of spinal cord circuitry because of their transparent early life stages and the striking anatomical and functional similarities between their spinal cords and those of humans.[85-87]

Approximately 10% of ALS cases are familial, indicating that they are caused by gene mutations, whereas 90% of cases are sporadic and have no known cause. Numerous clinically and morphologically distinct disease characteristics are shared by sporadic and familial ALS, such as progressive loss of motor neurons, paralysis, muscular atrophy, and early death.[88]

Over the past few years, there has been significant progress in unravelling the genetic frameworks of ALS, with the identification of disease-causing mutations in several genes, including those fused to superoxide dismutase 1 (*SOD1*), chromosome 9 open reading frame 72 (*C9orf72*), sarcoma (*FUS*), profilin 1 (*PFN1*) sequestosome 1 (*SQSTM1*), optineurin (*OPTN)*, and TANK-binding kinase.[89] These genetic breakthroughs have shed light on the cellular issues contributing to ALS development, such as oxidative stress, protein misfolding, cytoskeletal changes, mitochondrial dysfunction, and RNA metabolism dysregulation. Protein inclusions are pathogenic indicators of ALS in dying motor neurons.[89] Protein inclusion is a pathological indicator of ALS.

Table 1: Comparative study of zebrafish and human genes that are involved in Alzheimer's disease.

Common Name	Genes in Human	Genes in Zebrafish	Functions of Related Protein
Amyloid Precursor Protein	*APP*	*appa* *appb*	Synaptic formation and repair, β-amyloid generation, and neuronal development
Presenilin 1 Presenilin 2	*PSEN1* *PSEN2*	*psen1* *psen2*	γ- Synaptic plasticity, secretase activity, β-amyloid formation, and intracellular signaling
Apolipoprotein E	*APOE*	*apoeb*	Synaptic integrity, lipid transport, lipid and cholesterol metabolism, Aβ clearance, mitochondria regulation
Microtubule-Associated Protein Tau	*MAPT*	*mapta* *maptb*	Tau protein helps in the microtubule stabilization
Presenilin Enhancer 2	*PSENEN*	*psenen*	Gamma-secretase subunit PEN-2 A protein called PEN-2 is produced under instructions derived from the PSENEN gene. This protein is a part of the complex known as the gamma-(γ-) secretase.

SOD1 gene mutations account for 20% of all ALS cases.[90-92] In zebrafish larvae, *SOD1* mutant overexpression resulted in anomalous neuromuscular junctions that worsened with age in fish.[93] In zebrafish larvae, *sod1* shows a gradual reduction in neuromuscular junction volume, decreased performance in the forced swim test, and weakened responses to repeated stimulation.[93] In contrast to defects in the intrinsic properties of the muscle, these factors suggest an issue with the neurological input to the muscle cells.[93] Zebrafish can be useful for tracking the development of ALS manifestations, but genetic mutations and pharmaceutical models can also be used to pinpoint the disease's molecular causes. For instance, the loss of function of the *C9orf72* orthologue in zebrafish causes motor neurons to axon degenerate, which is followed by a reduction in the swimming and moving abilities of larval zebrafish.[94] *C9orf72* is implicated in ALS and

other neurodegenerative illnesses due to motor impairments caused by *C9orf72* knockdown.[94]

The *FUS* gene, which encodes the multifunctional protein Fused-in-Sarcoma/Translocated in Liposarcoma, is linked to ALS. It is found in RNA encompassing stress granules and is involved in anabolism as well as in catabolism of RNA.[95-100] Since 2009, several *FUS* gene mutations have been concomitant with ALS.[100-105] Numerous mutations alter the nucleus location of *FUS*, affecting its ability to regulate transcription and RNA processing and leading to hazardous FUS clusters in the cytoplasm.[106-110]

TAR-binding protein 43, commonly abbreviated as TDP-43, a key component of neuronal inclusions in patients with ALS and frontotemporal dementia, plays a critical role in RNA metabolism, including miRNA processing, mRNA stability, and the regulation of splicing.[111-114] More than 50 distinct point mutations in the TARDBP gene, which encodes TDP-43, have been associated with ALS. More than 50 distinct point mutations in the *TARDBP* gene, which encodes TDP-43, have been associated with ALS, altering its transport function between the nucleus and cytoplasm, modulating cellular functions, and influencing aggregate formation and disease progression.[103-104, 115]

Motor neuron axonopathy caused by the production of mutant *tardbp* in zebrafish embryos was prevented by coexpressing wild-type human *TARDBP* genes but not the mutant form.[116] The "distal axonopathy" theory of ALS, which proposes that pathological changes occur at the neuromuscular junction during the presymptomatic phase of the disease, was recently confirmed in zebrafish.[117] Zebrafish *TDP-43* knockdown caused early impairment of motor ability and disintegration of the neuromuscular connection. Additionally, scientists have demonstrated that acetylcholinesterase expression is affected by partly depleted *TDP-43*, indicating that this enzyme is a limiting component in the regulation of links between muscle and motor neurons.[117] Ciprofloxacin and celecoxib combination therapy improved locomotor and cellular deficits in an ALS zebrafish model. The results of this study identified a novel combination that was effective for the treatment of ALS and demonstrated the utility of zebrafish for the therapeutic development of ALS.[118]

The utility of zebrafish in ALS research has several limitations similar to those of other model systems. Some of these limitations include the absence of the predominant use of embryonic stages, the unavailability of zebrafish specific antibodies for research inquiries and upper motor neurons.[119,120]

In summary, there are benefits and drawbacks to using rodents and zebrafish as model organisms in research. The particular goals and components of the biological system under study will determine which of these two approaches is optimal. The similarities and differences between these animals, as well as the practical issues related to their use in experiments, must be considered by researchers (Table 2).

Anxiety and Depression

In today's world, stress is common and affects the bodily and mental processes. It improves memory and performance and boosts alertness, attention, and vitality to a limited extent.[121] Chronic stress, on the other hand, has detrimental consequences on the body and the mind, which can lead to disorders including anxiety, depression, panic attacks, phobias, and adjustment disorders, as well as negatively impacting productivity and quality of life.[122,123]

Table 2: - Benefits and drawbacks of using rodents and zebrafish as an animal model.

Model Organism	Why it is used as an animal model	Why it is not used as an animal model
Zebrafish	Human CNS and neurotransmitters are similar to zebrafish	Upper motor neurons are lacking
Rodents	Human CNS and neurotransmitters are very similar to rodents	There is time-consuming investigation and high animal maintenance costs

Within mammals, the hypothalamus triggers a stress response by activating the HPA axis, which then communicates with the pituitary gland and the adrenal medulla.[124] Except for the adrenal medulla, which mainly consists of inner cells called the adrenal cortex, the functions of the hypothalamus, pituitary, and adrenal cortex, the three main constituents of the HPA axis, are comparable to those of the HPI axis in zebrafish (Fig 4).[125] Stress triggers a coordinated response in zebrafish that releases cortisol into the blood through the HPI axis.[126] This response is instigated by the activation of the hypothalamus due to stress, leading to the release of Corticotrophic Releasing Factor (CRF).[127,128] CRF subsequently stimulates the anterior pituitary gland to produce and secrete adrenocorticotrophic hormone (ACTH) into the bloodstream.

Proopiomelanocortin-encoded proteins undergo post-translational modifications to generate ACTH.[126,127] The melanocortin 2 receptor on steroidogenic cells in the inter-renal region is subsequently bound by ACTH, leading to enhanced production and release of cortisol.[127,129] Cortisol is the principal circulating glucocorticoid in zebrafish, and the tissue surrounding its adrenal glands resembles that of higher vertebrates.[130] As a result, cortisol remains the primary glucocorticoid present in the circulation of zebrafish. It enhances metabolic capacity and mobilizes energy reserves to ensure homeostasis in zebrafish.[127] Reduced glucocorticoid receptor expression is a result of ongoing stress and excessive HPA axis activity, which also decreases the body's capacity to adapt to and manage stressful situations.[131] This affects mood by making it harder to cope with stress related events, leading to depression.[132]

Chronic exposure to unpredictable mild stressors over an extended period in zebrafish may lead to depressive-like states.[133-135] It is reported that people with depression often show increased COX-2 transcription levels, which is thought to negatively impact cognitive function, mood, and synaptic balance.[136] Another study has shown that many psychiatric medications effectively reduce the expression of IL-6 and TNF-Alpha, indicating the model's sensitivity to these antidepressants.[134] Alternative therapeutic approaches, such as administering reserpine to zebrafish, elicit depressive-like responses in the fish, including social isolation, impaired motor function, and elevated cortisol levels that resemble

the symptoms of depression observed in clinical cases.[137] Several genetic models and methodologies have been used to study zebrafish behaviors similar to depression. A dysfunctional HPI axis was noted, leading to heightened physiological responses, such as elevated cortisol levels throughout the body. This stress reaction was observed in larval fish with mutant glucocorticoid receptors (GR) (gr/s357).[41]

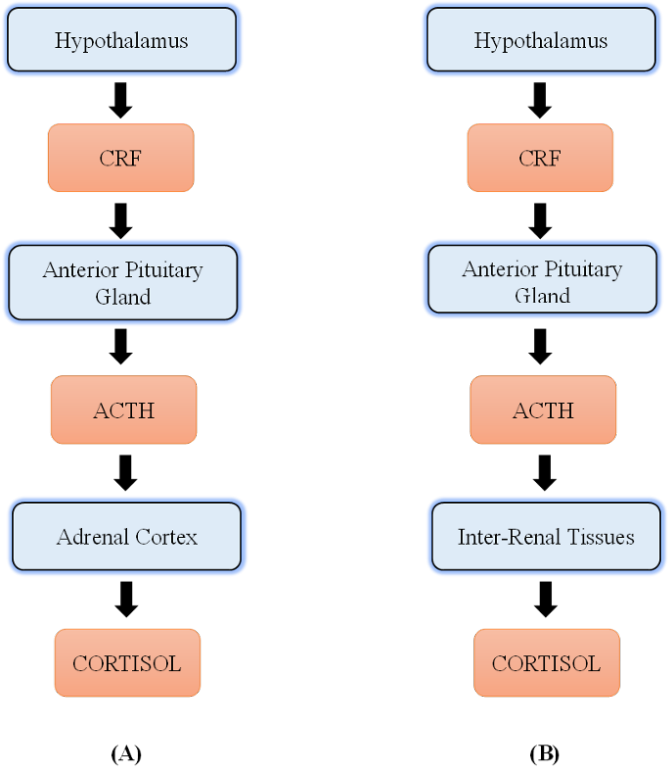

Figure 4: Illustration of (A) Mammals HPA axis, (B) Zebrafish HPI axis.

Zebrafish are increasingly becoming a favored model organism for investigating the impact of stress on early-life brain circuits and behavioral alterations in research.[138,139] The basic molecular and physiological elements of the human stress response are similar to those of zebrafish, notably, the production of cortisol [49,134,140] and studies of anxiety-related behavior in zebrafish provides a valuable understanding of anxiety disorders in mammals.[141]

Several classical anti-anxiety medications have been evaluated using zebrafish models. For instance, α- fluoromethylhistidine displayed anxiolytic effects [142], diazepam alleviated anxiety triggered by cocaine withdrawal, and the benzodiazepine inverse agonist FG-7142 provoked anxiety in zebrafish.[143]

Epilepsy

Over 70 million individuals worldwide suffer from epilepsy, a common neurological illness.[144] Despite receiving the best care, spontaneous seizures and other behavioral disturbances are elicited due to an imbalance in excitatory and inhibitory mechanisms.[145] Epilepsy patients usually suffer from psychological disability, cognition, pervasive social stigma, and premature death in addition to seizures.[144,145] Repeated convulsions or seizures, behavioral regression, abnormal brain activity, and endocrine malfunction are all symptoms of epilepsy.[146-149] The main behaviors associated with epilepsy are hyperactivity, inconsistent swimming, spasm-like corkscrew swimming, loss of body posture, and electrical discharges to the CNS.[150-152]

Epilepsy has a very varied etiology that includes both inherited and acquired origins. Approximately 60% of the time, there was no recognized reason. Young children and elderly individuals have the highest rates of epilepsy. Younger people are more likely to have genetically caused developmental and epileptic encephalopathies (DEE).[153] These findings are generally considered outcomes of a combination of genetic and environmental variables.[154]

The optimal animal model for epilepsy should mimic the genetic, metabolic, neuroanatomical, and electrophysiological aspects of human epilepsy. Rats are commonly employed as the standard experimental prototype for epilepsy; however, it is crucial to keep in mind that all animal models are comparative. It is necessary to choose the most appropriate and efficient epilepsy models based on their ability to mimic human seizures.[155] In 2005, zebrafish gained recognition as an ideal model for epilepsy research after it was found that they could display seizure characteristics induced by chemicals, similar to those observed in rats.[151] Thus, zebrafish with several advantageous qualities have solidified their position as a better option for epilepsy studies than conventional rodent models, such as mice (Table 3). They represent a viable option for the initial screening of remedies and genetic transformations associated with epilepsy.[156] Zebrafish are an excellent choice for modeling the developmental progression of epilepsy pathogenesis, mainly owing to their accelerated development and longer lifespan compared with mice (Table 3).

Table 3: Analysis of rodent and zebrafish efficiency as models of epilepsy.

Causes of Seizures/epilepsy	**Animal models**	
Human	**Rodents**	**Zebrafish**
Brain damage -Trauma -Tumor -Neuro-degeneration -Stroke	Good brain damage-induced seizure model	Good brain injury model available stroke model High regenerative ability
Febrile seizures	Good rodent models of febrile seizures	Hyperthermia leads to seizure in Zebrafish
Genetic factors -Risk factors -Monogenetic diseases -De novo mutations	Good genetic models	Good genetic models (eg. scn1lab, gabra1. depdc5, gabrg2) Expanding numbers due to the low cost and rapid generation of the new mutant lines.

Using acute doses of caffeine, pentylenetetrazole, and picrotoxin to trigger seizures in zebrafish leads to hyperactivity, corkscrew

swimming, spasms, and elevated cortisol levels throughout the body.[157] Antiepileptic medications reduce all of these symptoms in zebrafish larvae and adults.[143] In this way, when creating new antiepileptic medications, the zebrafish and its larvae can be great model organisms.

The Dravet model, which has a homozygous mutation affecting the sodium channel (*SCN1A*, orthologue gene is *scn1lab*), is the first and most thoroughly researched zebrafish model of epilepsy.[158] Zebrafish models of the *scn1lab* gene exhibit seizures and decreased function. Numerous manifestations have been observed, such as increased sensitivity to light stimuli, altered locomotor bouts, altered gene expression characteristics, and early larval death.[158-162]

The larval stage of zebrafish is frequently employed for screening high-throughput phenotypic drugs because of their small body size.[163] For instance, it was found that new compounds through selection in the scn1lab Dravet model lessen the elevated activity of locomotion brought on by the mutation.[158,159,164,165] Indeed, several of these compounds are already being tested in human clinical trials as antiseizure medications, demonstrating the enormous promise of this strategy.[166]

An autosomal recessive illness, EAST/SeSAME syndrome, is characterized by sensorineural deafness, epilepsy, renal tubulopathy, and ataxia, and has been linked to a decline in function by mutations in *KCNJ10* (codes for the inner-directed rectifying potassium channel Kir 4.1 that is expressed in glial cells in patients.[167-169]. Notably, in zebrafish, kcnj10 is a possible cause of the EAST/SeSAME syndrome.[152,170]

Table 4: Genetic mutant models of zebrafish and their respective behavioral phenotypes.

Genes in human	Genes in zebrafish	Epilepsy syndrome	Behavioural phenotype	References
SCN1A	*scn1lab*	Dravet GEFS+ (common epilepsy associated with febrile seizures plus)	Abnormal swimming ability, sensitivity to hyperactivity, hyperthermia, myoclonic jerks, convulsive behaviors, from the third day of post-fertilization in zebrafish	163,164,167
KCNJ10	*kcnj10*	Epilepsy, ataxia, renal tubulopathy and sensorineural deafness	aberrant facial and fin movements, seizures, ataxia, a sudden spike in activity and an imbalance in posture	157,175
KCNQ3	*kcnq3*	benign familial neonatal seizures (BFNS)	convulsions	181

Mutations in various genes responsible for encoding potassium channels have been linked to syndromes with early onset of epilepsy, such as benign familial newborn seizures (BFNS) and neuronal encephalopathies.[171,172] Furthermore, *KCNQ2* and *KCNQ3* gene mutations have recently been linked to severe epileptic encephalopathies.[173,174] These mutations have also been linked to early-onset epileptic syndromes like BFNS.[171] In the majority of cases, the mutations result in loss-of-function variants that reduce the seizure threshold. However, a recent study identified four distinct patients with loss-of-function mutations in the *KCNQ2/3* genes. Surprisingly, these mutations stabilize the channel in an active state while simultaneously disrupting network connectivity and increasing hyperexcitability (Table 4).[175] Research indicates that kcnq channels are expressed in the nervous system of larval zebrafish and may play a direct role in generating seizure activity.[176]

Psychosis

Psychosis is evident when motor neuron function and social behavior are affected by cognitive abnormalities.[177] Studies have shown that the body is vulnerable to psychosis due to environmental risk factors like stress and exposure to drugs of abuse at specific points during life, as well as genetic risk factors like chromosomal variations.[178, 179] It is distinguished by abnormal glutamatergic signaling resulting from the misuse of substances like cocaine, a dopamine transporter antagonist, and phencyclidine (PCP), which inhibits glutamate receptors, as well as amphetamine, which obstructs dopamine transporters. They all exhibit indications of psychosis.[180]

Glutamate is the main excitatory neurotransmitter in the CNS of vertebrates.[181] Alterations in glutamatergic signaling influence numerous biological processes, such as development and aging, cognitive functions like learning and memory, and responses to environmental changes.[182-185] The two primary types of glutamate receptors are ionotropic (iGluRs) and metabotropic (mGluRs). The CNS contains glutamate receptors, a class of ionotropic receptors (iGluRs) that consist of N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), and kainate (KA). These receptors play crucial roles in synaptic transmission and are essential for various neurological functions, including learning and memory. In healthy volunteers, phencyclidine and ketamine cause psychotic symptoms, which are antagonists of the glutamate NMDA receptor.[179]

Zebrafish have been reported to be exceptionally suitable for investigating the behavior and molecular neuropharmacology related to NMDA receptor blockade.[185] This suitability stems from their high fertility, physiological resemblance to mammals, versatility in accommodating various experimental methods, responsiveness to forward genetic screens and high throughput techniques.[185]

A zebrafish psychosis model can be induced by dizocilpine maleate (MK-801), a known NMDA receptor antagonist.[186, 187] When a minor, non-startling response is provided prior to the startling stimuli, the startle reaction is also dampened; this phenomenon is known as pre-pulse inhibition (PPI).[188] According to Braff [189] the main feature of psychosis is impairment in the PPI, which can be addressed with antipsychotic medication.[190,191] In

conclusion, the zebrafish is a good model for identifying regulatory genes and possible drugs in the context of antipsychotic treatment because of its startle response and associated brain circuits.

CONCLUSION

With the rising incidence of neurodegenerative diseases, there is an urgent need to discover an effective treatment for the disease. Animal models have traditionally been utilized in neuropsychiatric research to enhance our understanding of human diseases. They are crucial in identifying biological and molecular targets, intending to create safer and more effective treatments. In summary, we emphasize the importance of using zebrafish as a useful model organism for neuropsychiatric research to further our comprehension of disorders affecting the human central nervous system. Finding biological and molecular targets is essential for drug development and biomedical research because the end goal is to create safer, more efficient, and more affordable treatments. Zebrafish are useful tools for neurobehavioral and neuropsychiatric research because approximately 82% of their genome is orthologous to genes linked to human diseases. Zebrafish represent a novel and promising research model of animals that offers valuable insights into the etiology of numerous central nervous system disorders like Alzheimer's disease, Amyotrophic Lateral Sclerosis, anxiety and depression, epilepsy, and psychosis. Zebrafish are model organisms that have the potential to greatly advance our understanding of these intricate conditions. Current AD therapies can only temporarily improve learning and memory by maintaining the levels of ACh and cholinergic transmission by AChE inhibitors. Notably, zebrafish possess similar genes like *apoE*, *tau* and *APP* which are involved in amyloid beta production and tau protein dysfunction. In ALS, the FDA-approved medications (riluzole and edaravone) offer only a limited improvement in survival. The spinal cord of zebrafish resembles that of humans, and their embryo's transparency makes them an important model for Amyotrophic Lateral Sclerosis. Due to their sensitivity to psychiatric medications, the zebrafish can be used as a stress model to study brain function and behavior. The study of epilepsy has significantly advanced through the use of the zebrafish model, which facilitates the observation of seizure activity and the assessment of potential treatments. Finally, the evolutionary conservation of CNS characteristics between zebrafish and humans presents promising prospects for advancing translational neuroscience and drug discovery based on phenotypic traits.

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