

## Zebrafish: An *In Vivo* Model for the Study of Therapeutic Targets of Epilepsy

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### Abstract

Epilepsy is a common neurological disorder due to excessive brain cell activity. It is characterized by unpredictable seizures resulting in cognition. The release of abnormal electric discharge in the regions of the brain causes epileptic seizures. Neurotransmitters play an important role in normal functioning of the brain and thus alteration of these neurotransmitters are associated with epilepsy. Zebrafish model have recently become a focus for various neurological disorders because of its high genetic similarity when compared with those of humans. Zebrafish can be grown in large numbers and their embryos are optically clear allowing examination of individual genes. This review will look at the utility of the zebrafish in the study of various therapeutic targets of epilepsy such as GABA (gamma-aminobutyric acid), AMPA, NMDA (N-methyl-d-aspartate), histamine H3, and phosphodiesterases.

**Keywords:** epilepsy; seizures; neurotransmitters; zebrafish; therapeutic targets

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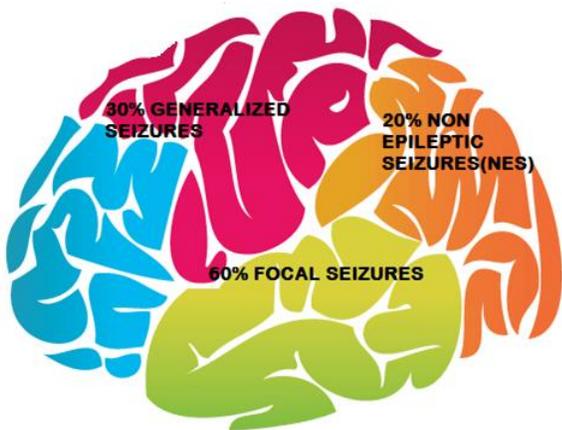
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### Introduction

Epilepsy is a common neurological disorder which causes biomedical disturbance resulting in abnormal electrical activity in certain neurons, which may further affect the entire brain. This abnormal neuronal activity has a significant influence in cognitive dysfunction and mental health condition (Kwan & Brodie, 2001; Meador, 2002; Smith, Craft, Collins, Mattson, & Cramer, 1986). An epileptic seizure is a sign of abnormal activity in neurons which is spontaneous. The effect of chemical reaction in the brain produces electrical discharges, and thus the disturbance of excitation and inhibition in a region of brain when moved too far in the direction of excitation results in seizures (Dekker, 2002).

The classification of epileptic seizures is divided into three categories (generalized, focal, and epileptic spasms) depending upon the release of abnormal electric discharge in the region of brain. Generalized seizures affect both hemispheres of the brain; focal seizures are limited to one hemisphere yet may progress to generalized seizures (Berg & Millichap, 2013). A seizure is accompanied with imbalance excitation and inhibition in the brain, resulting in alteration of brain functioning and genes. The imbalance leading to epilepsy can occur anywhere from circuit level to receptor level and, in some cases, it might be due to abnormal ionic channel function (Berkovic, 2015).



**Figure 1.** Classification of epileptic seizures upon abnormal electrical discharge in the human brain.

Both children and adults with epilepsy are prone to long-term forgetting in which newly acquired memories fade over days and memory impairment in which autobiographical or public facts are forgotten (Butler & Zeman, 2008). Accelerated long-term forgetting is a condition where individuals learn and initially retain information normally but forget the information at an unusually rapid rate (Blake, Wroe, Breen, & McCarthy, 2000). Accelerated forgetting has been demonstrated in both adults and children (Butler et al., 2009; Martinos et al., 2012).

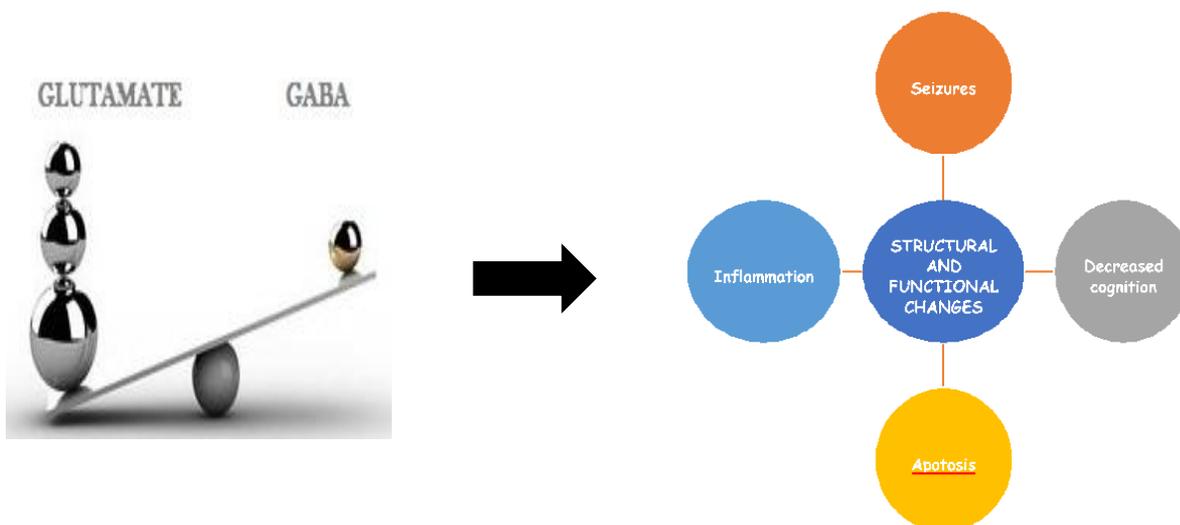
Neurotransmitters (gamma-aminobutyric acid [GABA], glutamate, and acetylcholine) are associated with normal functioning of brain. The alteration of

these neurotransmitters has a significant role in epilepsy (Sancheti, Shaikh, Khatwani, Kulkarni, & Sathaye, 2013). GABA is an inhibitory transmitter and helps in suppressing epilepsy, whereas glutamate causes neuronal death. Acetylcholine plays the key role in modulating glutamate release and memory formation (Ozawa, Kamiya, & Tsuzuki, 1998).

Zebrafish (*Danio rerio*) has become a widely used model system for the neurobehavioral system. Zebrafish are vertebrates and therefore more closely related to other model organisms and also share a high genetic similarity to humans; approximately 70% of all human disease genes have functional homologs in zebrafish (Cooper, D’Amico, & Henry, 1999).

Recent studies have proven that zebrafish possess several advantages over other animal models. Zebrafish are much easier to maintain in a laboratory and can also be grown in large numbers (Kimmel, 1989). The mode of fertilization is external, and their embryos are optically clear allowing examination of individual genes (fluorescently labeled or dyed; Bernasconi, 2004; Cendes, 2005; Kimmel & Warga 1988; Solnica-Krezel, Stemple, & Driever, 1995; Tran & Gerlai, 2015). The small size of zebrafish larvae allows easy manipulation of gene activities and screening of neuroactive compounds (Kuzniecky & Knowlton, 2002).

The aim of this systematic review summarizes the potential of zebrafish as a model organism to examine various therapeutic targets of epilepsy.



**Figure 2.** Schematic representation of excitatory and inhibitory neurotransmitter induced changes

## Therapeutic Targets of Epilepsy

### Gamma-Aminobutyric Acid

GABA is the major inhibitory neurotransmitter of the nervous system (Bowery & Smart, 2006). It acts through its receptors known as GABA receptors, which are divided into two classes, GABA<sub>A</sub> and GABA<sub>B</sub>. GABA<sub>A</sub> receptors are chloride channels, while GABA<sub>B</sub> receptors belong to class of G-protein coupled receptors (GPCR). GABA<sub>A</sub> receptors are combinations of 19 different subunits ( $\alpha$ 1–6,  $\beta$ 1–3,  $\gamma$ 1–3,  $\delta$ ,  $\epsilon$ ,  $\pi$ ,  $\theta$ , and  $\rho$ 1–3) and are targets for classes of clinically important drugs, such as benzodiazepines and barbiturates (Chua & Chebib, 2017; Möhler, 2006; Olsen & Sieghart, 2008).

GABA<sub>B</sub> receptors are G protein-linked receptors that decrease calcium entry and have a slow inhibitory effect. The activation of GABA<sub>B</sub> receptors is associated with a decrease in neurotransmitter release, and thus GABA<sub>B</sub> agonist drugs would have an antiepileptic effect (Swartzwelder, Bragdon, Sutch, Ault & Wilson, 1986). GABAergic neurons are ubiquitously distributed in the brain that determines the integration of all neuronal functions. Blockade of the fast inhibitory GABA<sub>A</sub> receptors might be the major cause of seizures. It has therefore been suggested that dysfunction of the GABAergic system may have an influence in the development of acute seizures and in the manifestation of epilepsy syndromes (Möhler, 2006).

Zebrafish contain at least 23 different GABA<sub>A</sub> receptor subunits. Although we observed some differences between the zebrafish and mammalian GABA<sub>A</sub> receptor subunit gene families, zebrafish contain orthologs for most of the GABA<sub>A</sub> receptor subunits found in mammals. GABA<sub>A</sub> receptors are expressed in larval zebrafish and are essential for normal brain function (Baraban, Taylor, Castro, & Baier, 2005).

### Ampa Receptor Potentiators

Glutamate is the major excitatory neurotransmitter released from nerve cells of the adult mammalian brain that mediates numerous processes. Glutamates are classified into two large subclasses of receptors: the ionotropic glutamate receptors and the metabotropic glutamate receptors. The ionotropic receptors can be further subdivided into AMPA, kainate, and N-methyl-d-aspartic acid (NMDA) receptors (Featherstone, 2010; Meldrum, 2000; Seeburg, 1993). The AMPA receptor comprises four subunits, which include at least two of the following subunit types: GluA1, GluA2, GluA3, or GluA4 (Mansour, Nagarajan, Nehring, Clements, &

Rosenmund, 2001). AMPA receptors are the major excitatory postsynaptic receptor which are expressed abundantly throughout the central nervous system (CNS; Rogawski, 2011).

Early studies have indicated the pathophysiologic role of AMPA receptors in epilepsy. The blockade of AMPA receptors may have a role in abnormal electrical activity in the epileptic brain (Mansour et al., 2001). The AMPA-receptor subunit expression of human epileptic brain revealed high expression of the GluA1-receptor subunit in the epileptic hippocampus (Graebenitz et al., 2011) which indeed increases the levels of homomeric GluA1 receptor, that exhibits high conductance compared with the GluA2-containing Ca<sup>2+</sup>-impermeable heteromeric receptors (Coombs, et al., 2012; Ying, Babb, Comair, Bushey, & Touhalisky, 1998). Neuronal degeneration usually occurs with increased expression of GluA2-lacking calcium permeable receptors, thus AMPA receptors might have a significant role in the pathophysiology of epilepsy: not only the expression of seizures but also the progression of epilepsy (Grossman, Wolfe, Yasuda, & Wrathall, 1999; Liu & Zukin, 2007; Swanson, Kamboj, & Cull-Candy, 1997).

The subunits of AMPA receptors have been expressed in zebrafish with a high degree of similarity when compared to those of humans, rats, and mice. AMPA receptors have been found in different regions of zebrafish (retina, hindbrain, spinal cord, and neurons; Ali, Buss, & Drapeau, 2000; Patten & Ali, 2007; Yazulla & Studholme, 2001). They are also associated with the neuromuscular junction that facilitate acetylcholine release during early development in zebrafish (Todd, Slatter, & Ali, 2004).

### N-Methyl-D-Aspartate Receptors

N-methyl-d-aspartate receptors (NMDARs) are ligand-gated ionotropic glutamate receptors that are important mediators for neuronal events such as synaptic plasticity, learning and memory, neuronal development and circuit formation, and have been implicated in various neuronal disorders (Cull-Candy, Brickley & Farrant, 2001; Hua & Smith, 2004). The mammalian NMDA receptor was first cloned in 1991 (Moriyoshi et al., 1991), and its structure and function has been studied widely in mammals. These receptors are highly permeable to calcium and, thus, may play important regulatory roles in the response of neurons to signaling (Mayer & Armstrong, 2004; Riedel, Platt, & Micheau, 2003).

There are five NMDA receptor genes expressed in mammals encoding for NMDAR1 (NR1) and NMDAR2 (NR2) subunits (Cox, Kucenas, & Voigt,

2005). The NR1 subunit are widely distributed throughout the CNS, which plays an important role in voltage independent zinc inhibition, whereas the NR2 subunits exhibit cell-specific expression patterns. Pharmacological regulation of the NMDAR depends on effects on unique combinations of subunit-specific binding sites. Both the NR1 and NR2 subunits contribute to the formation of the NMDAR ion channel. The glutamate-binding site is on the NR2 subunits, and the glycine-binding site is located on the NR1 subunits. The glycine (and/or D-serine) co-agonist site must be the pathogenesis of epileptic discharges (Carter, Deshpande, Rafiq, Sombati, & DeLorenzo, 2010).

The subunits NR1 and NR2 of NMDA receptor have been expressed in zebrafish and the similarity between subunits of zebrafish when compared to those of human showed high degree of identity (NR1 subunit expressed 90% identity and NR2 receptors expressed 50–90% identity; Cox et al., 2005).

### Histamine 3 Receptor Antagonists

The histamine neuroreceptor system is one of the major excitatory neurotransmitters exerting key neurological functions including alertness and sleep, seizure threshold, hormone secretion, and pain (Brown, Stevens, & Hans, 2001; Haas & Panula, 2003; Schwartz, Arrang, Garbarg, Pollard, & Ruat, 1991). Histamine belongs to a large superfamily of GPCRs that are characterized by the presence of seven transmembrane domains (Leurs, Bakker, Timmerman, & de Esch, 2005). The histamine H3 receptor (H3R), which is particularly expressed in the CNS and specifically in the brain, has led to the development of numerous antagonists/inverse agonists for the potential treatment of brain (Martinez-Mir et al., 1990). H3R is a presynaptic auto-receptor on histamine neurons and a heteroreceptor which modulates the activity of various neurotransmitters such as histamine, acetylcholine, noradrenaline, dopamine, serotonin, and GABA (Sander, Kottke, & Stark, 2008; Schlicker, Betz, & Göthert, 1988). Low levels of histamine are usually associated with convulsions (Kiviranta, Tuomisto, & Airaksinen, 1995; Tuomisto & Tacke, 1986).

The nonimidazole class has the potential to penetrate the brain more easily than those with an imidazole ring and, accordingly, H3R antagonists/inverse agonists have been targeted for a broad spectrum of brain diseases; for example, Alzheimer's disease, dementia, stroke, mood and sleep disorders, attention-deficit disorders, schizophrenia, narcolepsy, anxiety, depression, and epilepsy (Bahí, Sadek, Schwed, Walter, & Stark, 2013; Bhowmik, Khanam, &

Vohora, 2012; Inocente et al., 2012; Kuhne, Wijtman, Lim, Leurs, & de Esch, 2011; Leurs, Vischer, Wijtman, & de Esch, 2011; Sadek et al., 2013). Furthermore, ligands for the H3R are now in clinical studies and some companies have H3R antagonists for phase 1 and phase 2 clinical trials under review that could offer potential treatment for Alzheimer's disease, schizophrenia, epilepsy, narcolepsy, obesity, neuropathic pain, and allergic rhinitis (Micallef, Stark, & Sasse, 2013; Peitsaro, Sundvik, Anichtchik, Kaslin, & Panula, 2007).

Histamine receptors have been cloned and expressed in zebrafish in which H3R is expressed throughout the zebrafish brain especially in the region of optic tectum and hypothalamus, and receptor peptide sequence showed 50% identity in comparison to human (Griffin et al., 2017; Peitsaro, Anichtchik, & Panula, 2000). A recent study has demonstrated the role of clemizole (a histamine antagonist) as a potent inhibitor of seizures activity in zebrafish (Cofiel & Mattioli, 2006).

### Phosphodiesterases

Cyclic AMP (cAMP) and/or cyclic guanosine monophosphate (cGMP) are hydrolyzed by Phosphodiesterase (PDEs) that contains 11 isozymes encoded by 21 genes in mammals (Bender & Beavo, 2006; Seeger et al., 2003). PDE10A are found in multiple regions of the brain in mammalian species. The upregulation of cAMP and cGMP concentrations in different regions of brain is due to the inhibition of PDE10A (Francis, Blount, & Corbin, 2011; Grauer et al., 2009; Suzuki, Harada, Suzuki, Miyamoto, & Kimura, 2016). The presence of PDE10A in different regions of mammalian brain, suggests that it has various functions in the CNS (Leuti et al., 2013; Liddie, Anderson, Paz, & Itzhak, 2012). Several studies have clearly demonstrated the importance of PDE10A in the treatment of neurological and psychiatric disorders. The inhibition of PDE10A has proved as a promising candidate for the treatment of schizophrenia in animal or preclinical research (Siuciak et al., 2006). PDE10A may be involved in the pathophysiology of various neurological and psychiatric disorders (Giralt et al., 2013).

In zebrafish, 2',3'-cyclic-nucleotide 3'-phosphodiesterase was first reported as being induced during optic nerve regeneration study (Chang, Chandler, Williams, & Walker, 2010). Recent investigations have provided information of two enzymes of primary interest PDE4 and PDE10A which have a high percentage of identity to that of humans (Ballesterio, Dybowski, Levy, Agranoff, &

Uhler, 1999). Clearly more investigations are needed to elucidate the distribution of PDEs in fish and their role epilepsy.

## Conclusion

Animal models are considered as a useful tool for investigating the cause and pathology of human disease, yet to develop an animal model for brain disorder, particularly epilepsy, is very difficult because of its disease complexity. It is now recognized that zebrafish possess a great deal of similarity to mammals and are highly advantageous with their unique properties such as external fertilization, small size, as well as optical clarity of embryos. The central role of receptors in epilepsy demonstrates the potential utility of targets to control seizures. In this review we have discussed various pharmacological targets which are being investigated preclinically for epilepsy—GABA, Phosphodiesterase, Histamine 3, NMDA, and AMPA—and have illustrated the use of zebrafish in the assessment of these targets.

## Author Disclosure

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