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# Seizing the moment: Zebrafish epilepsy models

Kinga Gawel[a,b], Melanie Langlois[c], Teresa Martins[d], Wietske van der Ent[a], Ettore Tiraboschi[a,e], Maxime Jacmin[d], Alexander D. Crawford[d,f], Camila V. Esguerra[a,*]

[a] Chemical Neuroscience Group, Centre for Molecular Medicine Norway (NCMM), University of Oslo, Gaustadalléen 21, Forskningsparken, 0349, Oslo, Norway
[b] Department of Experimental and Clinical Pharmacology, Medical University of Lublin, Jaczewskiego St. 8b, 20-090, Lublin, Poland
[c] ML Consulting, 5 rue de Marseille, 69007, Lyon, France
[d] Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Belval, Luxembourg
[e] Neurophysics Group, Center for Mind/Brain Sciences, University of Trento, Piazza Manifattura 1, Building 14, 38068, Rovereto, TN, Italy
[f] Faculty of Veterinary Medicine, Norwegian University of Life Sciences (NMBU), Oslo, Norway

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ABSTRACT

Zebrafish are now widely accepted as a valuable animal model for a number of different central nervous system (CNS) diseases. They are suitable both for elucidating the origin of these disorders and the sequence of events culminating in their onset, and for use as a high-throughput *in vivo* drug screening platform. The availability of powerful and effective techniques for genome manipulation allows the rapid modelling of different genetic epilepsies and of conditions with seizures as a core symptom. With this review, we seek to summarize the current knowledge about existing epilepsy/seizures models in zebrafish (both pharmacological and genetic) and compare them with equivalent rodent and human studies. New findings obtained from the zebrafish models are highlighted. We believe that this comprehensive review will highlight the value of zebrafish as a model for investigating different aspects of epilepsy and will help researchers to use these models to their full extent.

## 1. Introduction

Epilepsy is a common, severe neurological disorder marked by recurrent abnormal synchronous activity in the brain (discharges), clinically characterized by either a sudden brief period of altered or lost consciousness, involuntary movements or convulsions (Thijs et al., 2019). Epilepsy is considered a spectrum disorder with highly diverse etiology, comprising both genetic and acquired causes. In about 60 % of cases the cause is unknown. The highest incidence of epilepsy is found in young children and in the elderly. Developmental and epileptic encephalopathies (DEE), resulting from genetic defects are more common in younger people (Stafstrom and Kossoff, 2016). In the majority of cases, these are believed to result from the interaction of multiple genetic and environmental factors. A lower number of cases are attributable to monogenic defects, with over 140 genes implicated to date (Ellis et al., 2020). Despite significant progress in understanding the molecular mechanisms of epileptogenesis, as well as the introduction of over 20 new antiseizure drugs (ASDs) since 1993, 30 % of patients remain resistant to currently available treatment options. This is especially true for rare epilepsy syndromes like Dravet, Lennox-Gastaut or West syndromes, which still have only a limited number of therapeutic options (Auvin et al., 2019).

Although there are now numerous rodent models of different types of epilepsies and epilepsy syndromes, the high cost of breeding and regulatory limitations in rodent experimentation reduces their use in drug screens. The models of pharmacoresistant epilepsy used by the NINDS Epilepsy Therapy Screening Program (ETSP) are well-validated, but the seizures in these models are induced chemically or electrically in the intact brain, and therefore do not mimic aspects of human epilepsy syndromes, which are of genetic origin (Löscher, 2017). Thus, there is a need for additional animal models that can aid the investigation of epileptogenesis, as well as provide *in vivo* drug screening possibilities.

Zebrafish (*Danio rerio*) have several advantages which makes this species a valuable model for neurobiology. A detailed description of the advantages of zebrafish in biomedical and in particular, epilepsy research, is provided in recent excellent reviews (de Abreu et al., 2019; Gawel et al., 2019; Sakai et al., 2018). Briefly, factors that make zebrafish an attractive research model are its simple breeding and maintenance requirements, high fertility, rapid external development, body transparency at the larval stage and a multitude of methods available for efficiently generating genetically modified strains. Furthermore, zebrafish share high physiological and genetic homology with humans, with over 82 % of disease-associated genes in humans having

* Corresponding author.
*E-mail address:* c.v.esguerra@ncmm.uio.no (C.V. Esguerra).

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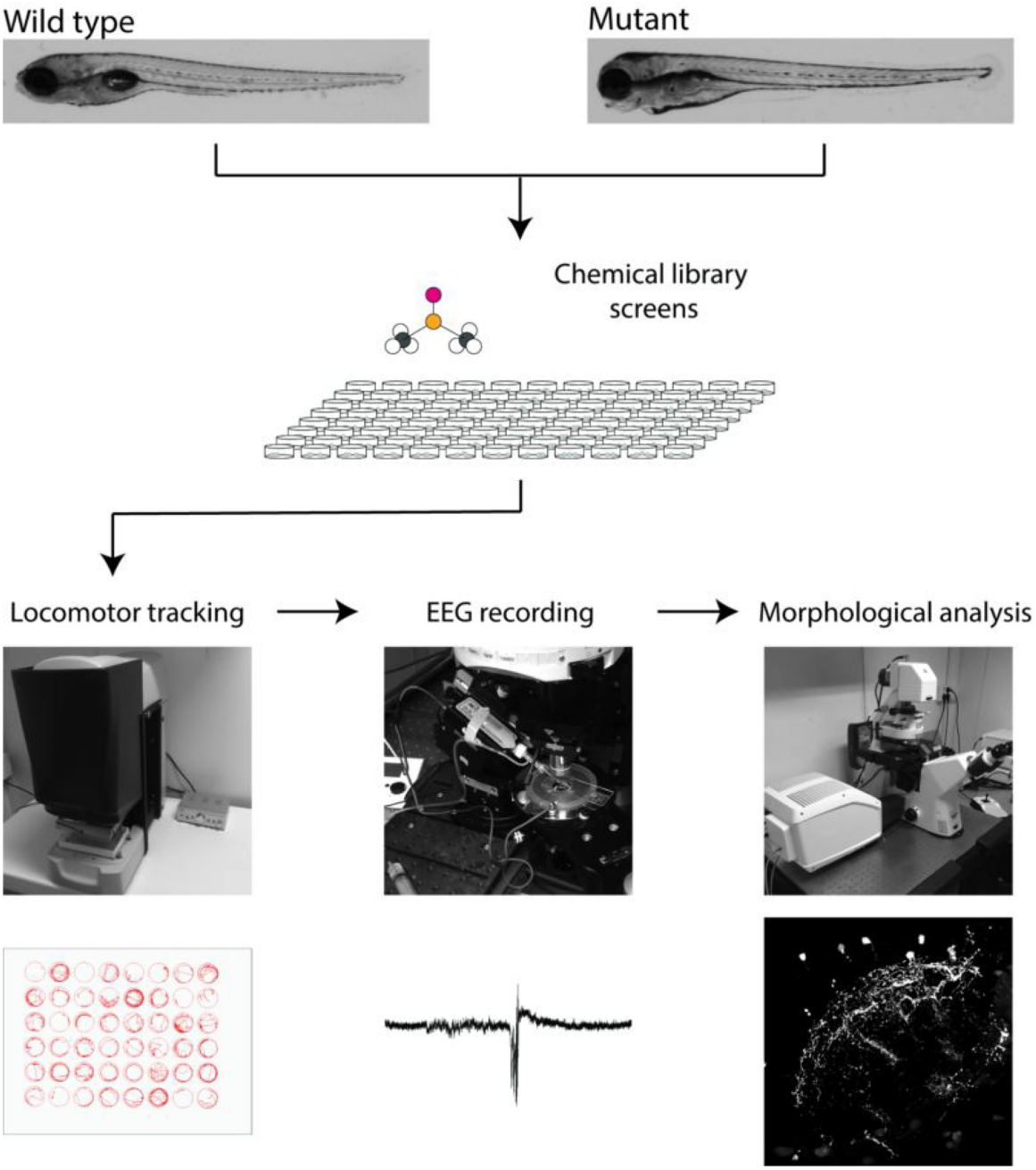


**Fig. 1.** Schematic representation of zebrafish bioassays used in epilepsy research.

identifiable orthologs in zebrafish (Howe et al., 2013). For epilepsy research, important advantages include the ability to perform (1) high-throughput behavioral analysis using automated video tracking systems, (2) electroencephalographic (EEG) recordings in both larval and adult fish, and (3) *in vivo* brain imaging by means of activity-dependent bioluminescent/fluorescent reporters (Afrikanova et al., 2013; Brenet et al., 2019; Dinday and Baraban, 2015; Naumann et al., 2010; Tiraboschi et al., 2020) (see Fig. 1). Altogether, these features make zebrafish a useful model for studying epileptogenesis and performing high-throughput screening of compounds with antiepileptic or anti-seizure potential.

In this review, we aimed to summarize existing knowledge about different pharmacological and genetic models of epilepsy/seizures in zebrafish and compare them with equivalent human and rodent studies. We describe the findings obtained from these models and also highlight gaps in existing knowledge. We believe that this comprehensive review will help researchers to better evaluate zebrafish as a model for investigating different aspects of epilepsy/seizures.

### 1.1. Pharmacological models

#### 1.1.1. Pentylenetetrazole

Pentylenetetrazole (PTZ) was one of the first proconvulsant drugs used in animal models to induce seizure activity (Porter et al., 1984). The mechanism by which PTZ induces seizure activity is not yet well-defined, but has been suggested to occur primarily by interfering with GABAergic neurotransmission (Macdonald and Barker, 1978) - a fast inhibitory synaptic transmission that is mediated by γ-aminobutyric acid (GABA) interaction with both ionotropic and metabotropic membrane receptors (Bormann, 2000). In the case of the ligand-gated ion channel $GABA_A$ receptor, this interaction results in the influx of negatively charged chloride ions, which contributes to fast neuronal

hyperpolarization. PTZ is a $GABA_A$ receptor antagonist (Macdonald and Barker, 1978) that binds to the transmembrane domain that lines the ionophore, increasing the closed state of the channel (Huang et al., 2001). This property may explain the resulting proconvulsant activity by enhancing neuronal excitation. Moreover, it explains why most ASDs that act on GABAergic transmission, such as diazepam, felbamate, phenobarbital, vigabatrin and tiagabine, are effective in the subcutaneous (s.c.) PTZ test (Bialer and White, 2010). However, PTZ can also interact and modulate the ionic conductance of voltage-gated potassium channels, favoring inactivation of those at slight negative-to-positive membrane potentials, thus further increasing neuronal depolarization (Madeja et al., 1996). Long-term effects of PTZ (for instance by repetitive administration) include the regulation of GABA and glutamate receptor expression and/or affinity (Schroeder et al., 1998; Walsh et al., 1999; Zhu et al., 2004), which may lead to an imbalance between excitation and inhibition in the brain and trigger epileptogenesis.

Over the last seven decades, the s.c. PTZ seizure test in rodents has been one of the most widely used models for ASD discovery and is generally predictive for compounds with activity against generalized absence and myoclonic seizures in humans (Porter et al., 1984; White, 1997). At single low-doses, PTZ induces experimental absence-like seizures, characterized by staring, behavioral arrest, occasional myoclonus, eye movements and automatisms, while increasing the dosage leads to tonic-clonic convulsions (Gallitto et al., 1987). Furthermore, repeated systemic administration of sub-convulsive doses of PTZ leads to development of kindling, a process that results in progressive seizure susceptibility and severity (Dhir, 2012). This model has been particularly suitable for studying long-term molecular, structural and functional changes in the brain induced by seizures (Morimoto et al., 2004). More recently, epilepsy research has been focused on the development of new PTZ-induced seizure models using simpler vertebrates, such as zebrafish, for high-throughput drug screening.

The PTZ model of zebrafish was first described 15 years ago by Baraban and collaborators, and later confirmed by subsequent studies, demonstrating that zebrafish larvae at 7 days post-fertilization (dpf) display behavioral, electrophysiological and molecular alterations similar to the rodent PTZ model (Afrikanova et al., 2013; Baraban et al., 2005). Seizure-like behavior is elicited in zebrafish larvae by immersion in a small volume of PTZ solution, which is presumed to be absorbed by the skin, gut or gills, eventually reaching the brain (Afrikanova et al., 2013; Baraban et al., 2007, 2005) (see Table 3). Changes in locomotor behavior are observed within a few seconds to minutes and is characterized by a sequence of events starting from rapid movements along the periphery of the behavioral chamber (stage I), followed by "whirlpool-like" movements (stage II), and in case of higher PTZ concentrations, seizure-like behavior culminates with alternating periods of brief pauses and rapid, jerky movements as well as occasional body-stiffening and loss of posture (stage III) (Afrikanova et al., 2013; Baraban et al., 2005). This PTZ-induced locomotor behavior correlates with brain electrical activity determined by EEG, and is characterized by spontaneous epileptiform discharges with amplitude, frequency and duration features that vary with the timing of PTZ exposure (Afrikanova et al., 2013; Baraban et al., 2005) Importantly, the convulsive behavioral and epileptiform discharges are counteracted by standard ASDs such as valproic acid and diazepam (Afrikanova et al., 2013; Baraban et al., 2005; Berghmans et al., 2007; Watanabe et al., 2010) (see Table 1). Examples of EEG discharges are given in Fig. 2, and Box 1 provides an overview of the effect of different PTZ concentrations on larval behavior.

PTZ likely induces generalized seizures in the zebrafish brain as the expression of *c-fos* and phosphorylated extracellular signal-regulated kinase (ERK) are observed in different brain compartments as early as 15 min after PTZ incubation (Baraban et al., 2005; Baxendale et al., 2012; Buenafe et al., 2013; Randlett et al., 2015). The expression of these genes, which is fast and transient after neuronal activation, is well accepted as a marker for regions of seizure generation and propagation in the brain (Houser et al., 2012; Morgan et al., 1987). Furthermore, intracellular calcium transients are observed in different brain compartments of calcium–reporter zebrafish lines treated with PTZ (Naumann et al., 2010). The mechanism of seizure generation by PTZ is likely similar to the rodent model, as GABAergic and GABA-responsive neurons arise in discrete regions throughout the different brain compartments at early embryonic stages (Baxendale et al., 2012; Doldán et al., 1999; Higashijima et al., 2004; Martin et al., 1998) and are highly represented in forebrain, midbrain and hindbrain areas at the larval stage (Higashijima et al., 2004; Mueller et al., 2006; Smear et al., 2007).

**Table 1**
Pharmacological response observed in AG and PTZ animal models for commonly-used ASDs (Afrikanova et al., 2013; Ashton and Wauquier, 1979; Baraban et al., 2007, 2005; Berghmans et al., 2007; Bialer and White, 2010; Leclercq et al., 2015; Löscher, 2017; Watanabe et al., 2010).

| ASDs | Zebrafish PTZ | Zebrafish AG | Rodent PTZ | Rodent AG |
|---|---|---|---|---|
| Carbamazepine | – | NA | – | NA |
| Diazepam | + | + | + | + |
| Ethosuximide | + | NA | + | + |
| Gabapentin | – | NA | – | NA |
| Lamotrigine | – | NA | – | NA |
| Levetiracetam | – | – | + (SWDs) | – |
| Oxcarbazepine | – | NA | +/- | NA |
| Phenytoin | – | – | – | – |
| Tiagabine | + | NA | + | NA |
| Topiramate | – | + | – | – |
| Valproate | + | + | + | + |
| Zonisamide | – | NA | + | NA |

Abbreviations: - = no efficacy; + = proven efficacy; +/- = conflicting data; NA = data not available; SWD = spike and wave discharges.

Acute seizures can also be induced by PTZ in adult zebrafish (Lee et al., 2010; Pineda et al., 2011; Wong et al., 2010). Behavioral changes are observed shortly after exposure to PTZ in the water, or alternatively by PTZ intraperitoneal (i.p.) injection (Banote et al., 2013; Mussulini et al., 2013; Wong et al., 2010). Exposure is followed by a sequence of events that is dependent on PTZ concentration and duration of exposure, and generally starts with hyperactivity-like behaviors and circular movements, followed by tonic-clonic-like seizures characterized by spasms/contractions and loss of posture (Banote et al., 2013; Mussulini et al., 2013; Wong et al., 2010). EEG recordings in the adult zebrafish confirmed the proconvulsant activity of PTZ, showing epileptiform-like discharges similar to the rodent and human EEG profiles (Banote et al., 2013; Pineda et al., 2011). Moreover, as observed for zebrafish larvae, *c-fos* expression in the adult zebrafish brain is increased and ASDs that are effective in rodent and larval zebrafish models, such as diazepam and valproic acid, also show activity in the adult zebrafish seizure model (see Table 1) (Lee et al., 2010; Mussulini et al., 2013). Additionally, a first model of PTZ-induced kindling was developed in adult zebrafish (Kundap et al., 2019). In this study, PTZ was administered at a daily dose of 80 mg/kg (i.p. infusion) for 10 consecutive days. The authors showed that small doses of PTZ gradually increased seizure score, starting at day 4 of administration. The scores ranged from 1.5 at day 5 to score 5 at day 10. Taking into account that this is the first report of a PTZ-kindling model in adult zebrafish, further studies are needed to determine its strengths and limitations.

PTZ-induced acute seizure models in larval and adult zebrafish have been employed for different purposes. The PTZ larval zebrafish model has been primarily used for screening and identification of small-molecule and natural compounds with potential anti-seizure activity (Baxendale et al., 2012; Buenafe et al., 2013; Challal et al., 2014; Orellana-Paucar et al., 2013). Importantly, some of these compounds also show activity in mouse models of epilepsy (Buenafe et al., 2013; Orellana-Paucar et al., 2013; Rahn et al., 2014), thus confirming the utility of the zebrafish as a fast and reliable model for primary ASD

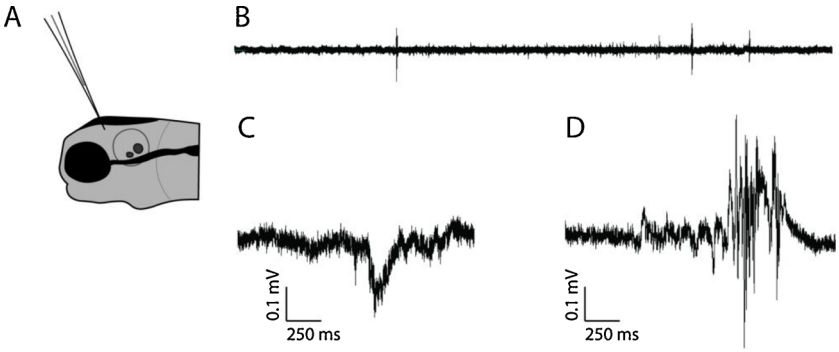


**Fig. 2.** Representative EEG recording from a mutant 7 dpf larva (B). A twenty minute-long recording was obtained from the larval optic tectum (A). An example of interictal-like (C) and ictal-like (D) discharges.

screening (see Table 1). Additionally, due to the genetic tractability of zebrafish, the PTZ larval model has allowed the rapid screening and identification of seizure-modulating genes, using both genetic mutant zebrafish lines and gene knockdown with antisense morpholino oligomers (MOs) (Baraban et al., 2007; Johnson et al., 2015; Mei et al., 2013; Teng et al., 2011). The adult zebrafish PTZ model, on the other hand, has proven utility in uncovering and characterizing complex seizure-like behavioral phenotypes that are difficult to assess in larvae (Gupta et al., 2014; Wong et al., 2010). Moreover, it has shown applicability in the study of behavior-related co-morbidities associated with epilepsy such as learning impairment (Lee et al., 2010), as well as in the investigation of cellular/molecular changes associated with seizure activity (Braida et al., 2012; Siebel et al., 2011, 2013, 2015a, 2015b).

### *1.1.2. Allylglycine and ethyl ketopentenoate*

(D,L)-allylglycine (AG) acts as a GABA synthesis inhibitor through irreversible inhibition of glutamic acid decarboxylase (GAD). Its effect is thought to be mediated by its main active metabolite, 2-keto-4-pentenoic acid (KPA) (Horton, 1978). In rodents, administration of AG has been shown to decrease the levels of GABA (up to 50 %) and increase glutamine concentration (40–70 %) in the brain (Chapman, 1985; Chapman et al., 1984; Taberner and Keen, 1977) whereas cortical GAD levels were significantly decreased in epileptic patients with drug resistant seizures (Lloyd et al., 1986). This compound was first reported more than 40 years ago for the induction of behavioral epileptic seizures in rodents and baboons (Ashton and Wauquier, 1979; Horton and Meldrum, 1973; Meldrum et al., 1974). In rats, administration of AG at doses ranging from 100 to 250 mg/kg was able to induce focal and generalized tonic extension seizures with a latency to first seizure ranging from 60 − 80 min after injection (de Feo et al., 1985; Thomas and Yang, 1991). In photosensitive baboons, AG was used at sub-convulsive doses to enhance the effect of photostimulation and lower the epileptic threshold (Chavoix et al., 1991; Horton and Meldrum, 1973).

Surprisingly, no attention was paid to AG in subsequent decades, likely due to the development and increasing popularity of the PTZ-based models for epileptic disorders. More recently, Leclercq et al. (2015) characterized the AG model and assessed the anticonvulsant effect of several ASDs on AG-induced seizures in both mice and zebrafish.

In 7-dpf zebrafish larvae, incubation with concentrations of AG ranging from 50 to 300 mM leads to an increase in locomotor activity characterized by behavioral stage I to III seizure-like events, as previously described by Baraban et al. (2005) for PTZ-induced seizures. In the vast majority of larvae, the latency to first seizure occurs between 90 and 120 min after incubation at the highest concentrations (200 − 300 mM AG) before leading to the unavoidable death of all fish from 180 min onwards. This increased motility is correlated with (1) a decrease in the GABA levels whereas the glutamate levels remain unchanged, leading to a significant reduction of the GABA/glutamate ratio and (2) the occurrence of epileptiform polyspiking discharges recorded with EEG in the larval optic tectum. These paroxysmal events were shown to occur with a mean frequency of about 16 events per 10-min recording, lasting 700 msec on average (Leclercq et al., 2015).

This AG-induced seizure model has been used to characterize the pharmacological responsiveness of zebrafish larvae to five ASDs with different mechanisms of action: co-administration of 300 mM AG with diazepam, sodium valproate or topiramate for two hours induces a significant decrease in the locomotor response, whereas levetiracetam

**Box 1**
The effect of different PTZ concentrations on larval behavior.

When using the PTZ assay in larval zebrafish, most authors have determined concentrations of 15 or 20 mM optimal for inducing EEG discharges with a concomitant increase in basic locomotion (Afrikanova et al., 2013; Baraban et al., 2005; Nieoczym et al., 2019). Baxendale et al. (2012) tested different concentrations of PTZ in 2-day-old larvae (up to 80 mM) and observed only a slight increase in larval distance travelled between concentrations of 15 and 20 mM. Indeed, when higher doses were used, the distance travelled decreased or returned to basic level (for 40 and 80 mM, respectively). In other words, the peak for increased locomotion was reached at 20 mM. Also, Berghmans et al. (2007) reported the same concentration-dependent pattern in 6-dpf larvae. In his original paper, Baraban et al. (2005) used the dose of 15 mM PTZ in 7-dpf zebrafish. More recently, Moradi-Afrapoli et al. (2017) aimed to optimize the PTZ dose used for induction of seizures in 7-dpf larvae. They observed a linear concentration-dependent response up to 10 mM, and a quadratic concentration-response up to 20 mM. When the data were plotted as movement in mm vs time, the changes in locomotor activity in subsequent time intervals were concentration dependent. Exposure to 5 mM PTZ increased distance moved in all 6 time points (5 min intervals; total 30 min observation) slightly, compared to control-treated group, but remained constant throughout the observation period. A concentration of 10 mM gradually increased the distance moved up to 15 min, while keeping it constant after reaching a peak. The concentrations of 15 and 20 mM PTZ almost immediately increased zebrafish locomotion for the first 15 min of observation, while a rapid decline was observed within the next 15 min. Although these data clearly confirmed the effectiveness of highest doses tested for rapid induction of hyperlocomotion, they also provided clues for proper analysis of data. Indeed, when analyzing the locomotor data, not only total distance travelled by zebrafish in 30 min long observation period should be analyzed. Rather, analysis of changes in behavior at different time intervals provides more valuable insight into the activity of compounds tested in the PTZ locomotor assay (Afrikanova et al., 2013; Challal et al., 2014; Nieoczym et al., 2019) (for example of the data, see Fig. 3).

and phenytoin do not show a suppressive effect. Similarly, co-administration of diazepam, sodium valproate, topiramate and to a lesser extent phenytoin, decreases the number and cumulative duration of epileptiform events induced by AG, as measured *via* intracerebral recordings. Conversely, only levetiracetam fails to achieve seizure reduction (Leclercq et al., 2015).

When compared to other commonly used preclinical models (i.e. PTZ or picrotoxin) and to the AG model in rats (Horton, 1978; Horton and Meldrum, 1973) or mice (Leclercq et al., 2015), the zebrafish AG model shows a unique responsiveness to ASDs classically used in clinical practice (see Table 1).

More recently, a new zebrafish model of drug-resistant epilepsy has been proposed using the AG derivative ethyl ketopentenoate (EKP) (Zhang et al., 2017). EKP is a lipophilic ethyl ester of KPA, the *in vivo* deaminated metabolite of AG. Similar to AG, EKP is an inhibitor of GAD. *In vivo* studies showed that EKP, compared to AG, has a stronger inhibitory effect towards GAD (Ki value of $10^{-6}$M and 50 mM, respectively) (Zhang et al., 2017). In mice, it was previously shown that intracerebroventricular administration of KPA lowered the threshold for induction of seizures at least 26-fold compare to AG (Horton, 1978).

In zebrafish, three orthologs of the *GAD1* and *GAD2* genes have been described i.e. *gad1a, gad1b* and *gad2*, sharing c.a. 76 % homology with human equivalent genes. Their proteins were found in the brain and spinal cord of developing zebrafish embryos, mediating local GABA synthesis (Higashijima et al., 2004; Martin et al., 1998). Zhang et al. (2017) revealed that expression of both orthologs was quite low at 1 dpf, increasing significantly to 3 dpf, while being constant at later stages. In their study, the authors showed that 7-dpf zebrafish exposed to 200 − 300 μM EKP displayed a dose-dependent increase in locomotion, while a dose of 400 μM substantially increased locomotion during the first 30 min of observation, culminating in death. EEG analysis, *c-fos* expression and neuroluminescence confirmed that EKP-induced hyperlocomotion was due to abnormal brain activity. In the last set of experiments, they evaluated their model using 14 commercially available ASDs. Among them, only perampanel proved to be effective in all three assays. Although EKP seems to be a promising zebrafish model of drug resistant seizures, it needs further validation.

### 1.1.3. Kainate

Kainic acid (KA) is a potent agonist of AMPA/KA glutamatergic receptors known to induce excitotoxicity, neuronal death and network reorganizations in various areas of the brain. Thus, KA remains one of the most widely used proconvulsant drugs to induce both acute seizures (by systemic injections) and recurrent seizures as a chronic model of temporal lobe epilepsy (by intracerebral injections) (Langlois et al., 2010; Löscher, 2017; Riban et al., 2002; Williams et al., 2007) in rodents.

In zebrafish larvae (5 and 15 dpf), 200 μM KA significantly reduces cell proliferation in a wide range of brain areas (Kim et al., 2010), and 50 μM KA generates EEG discharges characterized by short duration interictal events (100 − 200 msec) and long lasting bursting discharges (4 − 5 sec) occurring 8 times per minute on average. However, a more recent study led by Menezes et al. (2014) has shown that early exposure of larvae to KA induces decreased locomotor activity at 7 dpf (100–500 μM), an increased locomotion at 15 dpf (500 μM) without any behavioral expression typical of convulsive seizures in fish (stage V-VII, (Alfaro et al., 2011; Baraban et al., 2005)), and no effect on 30 dpf fish (Menezes et al., 2014). Moreover, pre-exposure to KA at 24 h post-fertilization (hpf) reduces the susceptibility of juvenile fish (60 dpf) to generate convulsive seizures when later exposed to KA (i.p. injection).

In adult zebrafish (3–6 months old), KA triggers convulsive seizures at doses ranging from 1 to 8 mg/kg, characterized by different behavioral stages: non-convulsive for stage I-IV, convulsive for stage V-VII (Alfaro et al., 2011). Whereas low doses (1–4 mg/kg) only induce non-convulsive epileptiform events, higher doses (6 and 8 mg/kg) lead to more severe clonic convulsions and subsequent death when stage VII is reached. In the same way, the latency to the first stage V seizure is significantly reduced at doses above 6 mg/kg, compared to low doses. At the maximum dose, fish display status epilepticus (SE), with a mortality rate around 20 %. The occurrence of such behavioral seizures is inhibited by concomitant injection of DNQX, a selective AMPA/KA receptor antagonist, and to a lesser extent by MK-801, a non-competitive NMDA receptor antagonist, thereby confirming a selective and highly specific activation of AMPA/KA receptors (Alfaro et al., 2011).

Recently, Mussulini et al. (2018) aimed to analyze the correlation between brain glutamate uptake biomarkers and the progression of behavioral changes (total distance travelled, number of mobile events and immobility time) in adult zebrafish exhibiting KA-induced post-SE. The authors focused on changes in the glial fibrillary acidic protein (GFAP), which may affect the function of excitatory amino acid transporters, at the level of brain damage biomarker- calcium-binding protein (S100B) as well as extent of glutamate uptake. They found behavioral arrest and lethargy 12 h after SE, whereas immobility time decreased substantially in subsequent time points (24, 72, 96 and 168 h after SE). From neurochemical point of view, they found time-dependent changes i.e. reduced uptake of glutamate in zebrafish forebrain and reduced level of GFAP-positive cells between 3 and 12 h after SE, and a reduced level of S100B up to 72 h after SE. These results clearly confirmed that neurochemical changes in zebrafish forebrain after SE are similar to those seen in equivalent rodent models. Furthermore, when using KA in adult zebrafish to study these alternations, there is a need to investigate them in specific time-windows.

Altogether, above-mentioned data suggest that KA can be used in zebrafish to induce epileptic seizures in both larvae and adult fish. However, the outcome and behavioral expression of seizures seems highly dependent on the time of exposure, limiting the potential of this model for high-throughput drug screening. Moreover, only little pharmacological data is available and further development is needed to better characterize the responsiveness of these KA-induced seizures to commonly used ASDs.

### 1.1.4. Other proconvulsant drugs: picrotoxin, pilocarpine, caffeine, ginkgotoxin, and strychnine

Besides the models described above, a number of other proconvulsants previously described in rodent models have been assessed in zebrafish.

Picrotoxin is a non-competitive $GABA_A$ receptor antagonist, known to induce tonic and/or clonic seizures in various species including rats and mice (Reza et al., 2009; Stöhr et al., 2007; Velísek et al., 1995; White et al., 2012). In zebrafish, incubation of 2-dpf larvae with 300 μM picrotoxin induces an increase in the expression of *c-fos* in the forebrain 60 min after treatment, consistent with the behavioral expression of seizures in zebrafish larvae, as previously described (Baraban et al., 2005; Baxendale et al., 2012). Moreover, this induction can be completely suppressed by concomitant administration of sodium valproate, thereby confirming that picrotoxin could also be used as early as 2 dpf to screen for new anticonvulsant compounds.

In adult zebrafish, a 20-min bath exposure to 0.17 mM picrotoxin results in behavioral seizures characterized by a specific alteration of locomotor activity expressed by reduced normal swimming interspersed with brief episodes of hyperactivity, occurrence of spasms, increased corkscrew and circular swimming (tonic-clonic behaviors), all representative of chemoconvulsant-induced seizures (Wong et al., 2010). However, little is known about the pharmacological responsiveness of this model to ASDs with different mechanisms of action, other than sodium valproate in larvae.

Pilocarpine acts as a muscarinic cholinergic receptor agonist, which has been shown to induce limbic seizures progressing to SE when given i.p. to rodents (Turski et al., 1983). To date, pilocarpine was only used in larval zebrafish, although there are discrepancies in the literature with regard to the time of exposure and the concentrations used for induction of seizures. For example, Vermoesen et al. (2011) used 30

mM pilocarpine at 7 dpf and the changes of locomotor activity were quantified manually for a period of 1 min. On the other hand, Lopes et al. (2016) used a range of doses from 15 to 60 mM and locomotor activity of 3-dpf larvae was measured for 18 min. Although both authors found that pilocarpine induced more subtle, epileptic-like changes in comparison to PTZ, this model still needs to be validated further.

Caffeine is a nonselective antagonist of adenosine receptors for which an overdose has been shown to induce epileptic seizures in humans and in various rodent models (Chrościńska-Krawczyk et al., 2011). In adult zebrafish, exposure to 1.3 mM caffeine induces a strong epileptic phenotype characterized by hyperactivity, spasms and increased corkscrew and circular swimming (Wong et al., 2010). Moreover, co-administration of low doses of caffeine with sub-convulsive doses of PTZ reduces the latency to first seizure, showing a synergistic and/or potentiating effect of caffeine (Gupta et al., 2014).

Ginkgotoxin is a neurotoxin found in *Ginkgo biloba*, a tree native to China, and is thought to prevent the synthesis of GABA and/or inhibit pyridoxal-5-phosphate (PTP), a cofactor involved in the biosynthesis of several neurotransmitters (Lee et al., 2012). Overdose of this natural product is known to elicit epileptic convulsions in humans (Leistner and Drewke, 2010). In zebrafish larvae, ginkgotoxin can induce seizure-like behaviors in a time and age-dependent manner, with a peak of severity at 3 dpf when larvae are incubated with 0.5 mM ginkgotoxin for two hours (Lee et al., 2012). These seizures were characterized by hyperactive and abnormal swimming. Interestingly, several ASDs including phenytoin, gabapentin and primidone have been shown to suppress such aforementioned seizure-like events (Lee et al., 2012).

Strychnine is a highly toxic alkaloid antagonist of glycinergic and cholinergic receptors, used for many years at low doses to induce convulsive seizures in rodents (Bum et al., 2001; Garba et al., 2015). More recently, short exposure of adult zebrafish to low-dose strychnine (5 mg/L, 5 min incubation) was shown to induce behavioral seizure-like activity including bursts of hyperactivity, spasms and increased circular swimming behavior, without affecting the total distance moved (Stewart et al., 2012). Again, more data about the pharmacological response of this model would be valuable to determine its ability to screen novel anticonvulsant compounds.

### 1.2. Genetic models

Among the current hypotheses related to epileptogenesis mechanisms, (i.e. the transition process from a normal to an epileptic brain), the most prevalent one has been the shift from inhibitory (i.e. GABA) towards excitatory (i.e. glutamate) neurotransmission (for excellent reviews see Crino, 2016; Lukawski et al., 2018; Kobylarek et al., 2020; Patel et al., 2019). Changes in GABA sensitivity, especially in the hippocampus, has been proposed as an underlying mechanism of epileptogenesis. In addition, other potential mechanisms have emerged, such as astrogliosis, inflammation, neuronal cell apoptosis or mTOR (mechanistic target of rapamycin) dysregulation. However, one should keep in mind that a large amount of data supporting these mechanisms were obtained from healthy animals in which epilepsy was induced chemically and were not investigated in animal models with specific gene mutations. Another important issue is that epileptogenesis is usually a long process in which the onset of seizures is preceded by a latent period. Thus, the active changes which eventually manifest in the form of convulsions, may take place months before any symptoms become apparent.

Although various rodent genetic models of epilepsy have been generated and investigated, due to a relatively long maturation period, it is challenging to trace changes in the rodent brain in short time intervals to find the optimal time for pharmacological intervention. Taking this into account, zebrafish epilepsy models may be especially useful for investigation of the epileptogenic process related to genetic mutations. Since symptoms of most epilepsy syndromes with genetic origin start to display in early childhood, the usage of larval zebrafish has proven very useful for monitoring brain changes during this period of development. For both pharmacological modulation and monitoring of changes in the brain, the rapid *ex utero* development and optical transparency of zebrafish is highly beneficial for determining the correct time window to focus on. Notably, there are zebrafish reporter lines (e.g. for GABAergic or glutamatergic neurons) which enable 3D visualization of neuronal branching in zebrafish brains by means confocal microscopy. Indeed, this allows for very quick and efficient tracing of dynamic changes in zebrafish brains and detection of the time window when the latent period develops into spontaneous seizures (Tiraboschi et al., 2020).

Regarding all MO models described below, one should keep in mind some limitations of MO-induced epilepsy models. There is prevalent concern within the scientific community surrounding the use of MOs due to their off-target effects, namely p53-mediated apoptosis. Thus, it is highly recommended to use a number of rigorous controls i.e. different types of MOs (splice- and translation blocking MO) to obtain the same phenotype, wild type mRNA rescue control experiments or a combination of MOs targeting the gene of interest with tp53-MO. Furthermore, if the gene of interest is duplicated, MOs targeting both paralogs are required to determine which of the paralogs is/are responsible for the phenotype. Furthermore, it is important to remember that the effect of MO is transient, lasting up to 5–6 days. Thus, only mutant lines are suitable for investigation of mutation-associated defects at later time periods. Lastly, some discrepancies between morphants and mutant phenotypes may occur due to compensatory mechanisms in mutant lines. Thus, MO-induced knockdown should be regarded as a preliminary test that should be validated in stable mutant lines.

Below, a detailed overview is given of the currently described epilepsy models in zebrafish. For a summary of characteristics of selected zebrafish mutants/morphants and zebrafish studies using EEG see Tables 2 and 3.

#### 1.2.1. SCN1A

Dravet syndrome is one of the most severe genetic epilepsies of infancy, characterized by the early occurrence of clonic febrile and afebrile seizures, followed by partial, myoclonic seizures, atypical absences and non-convulsive SE during the second year of life. Seizures persist most of the time as non-febrile, tonic–clonic attacks, are resistant to ASDs and are almost always associated with severe mental retardation (Genton et al., 2011). In over 80 % of cases, this syndrome is due to *de novo* mutations in the *SCN1A* gene, coding for the α subunit of $Na_V1.1$, a voltage-gated sodium channel (Claes et al., 2001; Guerrini, 2012; Mullen and Scheffer, 2009). To date, more than 600 mutations have been described in patients with generalized epilepsy with febrile seizures plus (GEFS + ) and Dravet syndrome (Claes et al., 2009; Mulley et al., 2005). A number of knockout mouse models carrying such mutations have been generated and recapitulate some of the key hallmarks of Dravet syndrome (Oakley et al., 2009; Yamakawa, 2011; Yu et al., 2006).

In zebrafish, the α subunit of the $Na_V1.1$ channel is encoded by the two homologous genes *scn1laa* and *scn1lab*, the latter -expressed in the CNS- showing 77 % identity with the human *SCN1A* gene (Novak et al., 2006b, 2006a). The first stable sodium channel mutant, $Didy^{s552}$, was identified in an ENU mutagenesis screen and carries a mutation in *scn1lab* (Schoonheim et al., 2010). $Didy^{s552}$ homozygous mutant larvae, viable up to 12 dpf, show abnormal swimming and hyperactivity concomitant with spontaneous convulsive behaviors from 4 dpf onwards, as well as dark pigmentation also observed in other larval epilepsy models. EEG recordings show two types of spontaneous epileptiform events: (1) interictal spikes (low amplitude, short duration) and (2) ictal-like epileptiform discharges (higher amplitude and duration) as early as 3 dpf, whereas sibling controls never show such behavioral and EEG paroxysmal events (Baraban et al., 2013). The pharmacological responsiveness of the $scn1lab^{-/-}$ mutant was also found to be very

**Table 2**
Behavioral and electrographic characteristics of select zebrafish mutants/morphants.

| Gene name /Zebrafish ortholog(s) | Stable mutant/ Knockdown | Epilepsy syndrome | Behavioral phenotype | EEG phenotype | References |
|---|---|---|---|---|---|
| *SCN1A / scn1lab* | Didy$^{s552}$/ *scn1lab* mutants/*scn1lab* morphants/ | Dravet GEFS+ | Abnormal swimming, hyperactivity, myoclonic jerks, convulsive behaviors, sensitive to hyperthermia, from 3 dpf | Spontaneous epileptiform events: interictal spikes and polyspiking discharges recorded in the forebrain. 1 – 1.5 event/min; ≈400 msec duration at 4 and 5dpf | (Baraban et al., 2013; Tiraboschi et al., 2020; Zhang et al., 2015) |
| *KCNJ10 / kcnj10* | NA / *kcnj10a/b* morphants | EAST/ SeSAME | *kcnj10a*: ataxia, seizure-like activity: burst of activity followed by a loss of posture; abnormal facial and fin movements | Clusters of spikes/poly-spikes. Frequency: 2 – 4 Hz | (Mahmood et al., 2013; Zdebik et al., 2013) |
| *KCNQ3 / kcnq3* | NA / *kcnq3* morphants | BFNS | Increase of locomotor activity, clonus-like convulsions | Paroxysmal discharges recorded with surface electrodes. ≈ 3 events /min, 300 – 400 msec duration | (Chege et al., 2012) |
| *STX1B / stx1b* | NA / *stx1b* morphants | Fever-associated epilepsy syndromes | Repetitive pectoral fin fluttering, orofacial movements, myoclonus-like jerks. No touch response at 4dpf | 2 types of bursting activity: polyspiking discharges (below 80 Hz) and HFOs (100 – 200 Hz frequency). 13 events/10 min, ≈ 100 msec duration | (Schubert et al., 2014) |
| *CHD2 / chd2* | NA / *chd2* morphants | Fever-sensitive myoclonic EE EMA | Abnormal movement patterns including whirlpool-like events, pectoral fin and jaw twitching, whole-body trembling. | Epileptiform discharges: multiple upward spikes with occasional ictal-like patterns in 4 dpf larvae | (Galizia et al., 2015; Suls et al., 2013) |
| *LGI1 / lgi1* | NA / *lgi1a/b* morphants | ADPEAF | *lgi1a*: morphological defects, hyperactivity, whirlpool swimming, myoclonic-like jerks *lgi1b*: morphological defects but no epileptic phenotype | NA | (Teng et al., 2011, 2010) |
| *CACNA1A/cacna1a/b* | NA/*cacna1aa* morphants | Absence seizures | Morphological changes, hypoactivity in light and dark phases | In 92 % of morphants abrupt spike-wave complexes, polyspike-wave discharges and high-voltage spikes at 4 dpf | (Gawel et al., 2020) |

Abbreviations: NA: not available; GEFS+: generalized epilepsy with febrile seizures plus; EAST/SeSAME: epilepsy, ataxia, sensorineural deafness and renal tubulopathy; BFNS: benign familial neonatal seizures; HFO: high frequency oscillation; EE: Epileptic encephalopathy; EMA: Eyelid myoclonia with absences; ADPEAF: Autosomal dominant partial epilepsy with auditory features.

similar to the one commonly seen in Dravet syndrome patients. In 5–6 dpf larvae, incubation with valproate, diazepam, potassium bromide or stiripentol significantly reduces the occurrence of epileptiform events, without affecting their mean duration (mean duration ranging from 200 and 600 msec) (Baraban et al., 2013). Conversely, most of the other ASDs such as acetalozamide, ethosuximide, phenytoine or vigabatrin had no suppressive effect on seizures. It is worth noting an aggravation of epileptic bursts with carbamazepine, ethosuximide and vigabatrin in this model (Baraban et al., 2013). In the same study, a phenotypic screen of 320 compounds revealed clemizole, a previously described and approved compound with anti-histaminic properties, as a promising entity with both behavioral and EEG anti-seizure activity in *scn1lab*$^{-/-}$ mutants (Baraban et al., 2013).

In the same way, the functional knockdown of *scn1lab* using antisense MOs leads to exacerbated sensitivity to hyperthermia (5–7 dpf) as well as behavioral and EEG impairments in zebrafish larvae aged 3–5 dpf (Zhang et al., 2015). This knockdown model displays morphological characteristics similar to the didy$^{s552}$ mutant such as hyperpigmentation and a slightly curved body axis (Baraban et al., 2013; Zhang et al., 2015). Spontaneous locomotor activity is significantly increased in MO-injected compared to control larvae, starting at 3 dpf up to 5 dpf. Interestingly, these abnormal behaviors are defined not only by sudden hyperactivity but also by movements resembling myoclonic jerks and tremors. The electrographic correlate of this hyperactivity is characterized by spontaneous epileptiform events in the brain. Indeed, local field potentials (LFP) recorded in the forebrain show polyspiking discharges in 80 % of the knockdown larvae (also referred to as morphants). Such paroxysmal events occured spontaneously 1–1.5 times per minute and lasted about 400 msec in 5-dpf larvae. The pharmacological profile of this model was confirmed and consistent with the stable mutant *scn1lab*$^{-/-}$, with a significant reduction of spontaneous behavioral seizures following exposure with clobazam, stiripentol, topiramate or sodium valproate, whereas carbamazepine induced a slight aggravation of hyperactivity at 4 and 5 dpf, compared to vehicle incubation and control larvae (Zhang et al., 2015). More importantly, this study showed for the first time the anti-seizure effect of fenfluramine in an animal model of Dravet syndrome. This potent serotonin releaser has already been described as an effective treatment when used as add-on therapy in Dravet patients (Ceulemans et al., 2012; Schoonjans et al., 2015). In zebrafish, fenfluramine significantly reduces the hyperactivity at 4 and 5 dpf. This decrease in the locomotor activity is strictly correlated with a specific inhibition of spontaneous and recurrent epileptiform events recorded in the forebrains of 5-dpf morphants. The occurrence of epileptiform events as well as the cumulative duration of paroxysmal events is dramatically reduced after incubation with either fenfluramine or sodium valproate, with lack of seizures in 29 out of 30 fish tested (Zhang et al., 2015). The anti-seizure effect of fenfluramine was recently confirmed in the didy$^{s552}$ stable mutant (Dinday and Baraban, 2015).

More recently, Brenet et al. (2019) characterized the excitatory/inhibitory synaptic balance in *scn1lab*$^{-/-}$ stable mutants, intercrossed with Gad1b and Vglut2a transgenic reporter lines. Labeling of PSD-95 (excitatory marker) and gephyrin (inhibitory marker) revealed an increase and decrease of these markers, respectively, showing a shift toward excitation. Moreover, the ratio of excitatory to inhibitory neurons increased at 4-, but not 3 dpf in *scn1lab*-depleted larvae.

Recently, our group investigated the early brain defects resulting from *scn1lab* deficiency in a new zebrafish model of Dravet syndrome (Tiraboschi et al., 2020). This new mutant line carries a missense mutation that was introduced by CRISPR/Cas9 mutagenesis and was designed to perturb ion transport function in all channel isoforms. Single-cell transcriptome analysis of 4- and 7-dpf *scn1lab*$^{-/-}$ larval brains revealed a progressive GABAergic neuronal loss and astrogliosis. A 40 % reduction of dendritic arborization in GABAergic interneurons of the optic tectum was observed in 6-dpf *scn1lab*$^{-/-}$ larvae. Chronic treatment of *scn1lab*$^{-/-}$ larvae with fenfluramine reversed these

**Table 3**
Selection of zebrafish studies using EEG.

| Study | Type of model | EEG type | Technical parameters | Readout |
|---|---|---|---|---|
| Baraban et al., 2005 | Pharmacological | Deep | Fish immobilized in 1.2 % agarose. Extracellular LFP recordings in the optic tectum. Glass microelectrode (2−7 MΩ) filled with 2 M NaCl. | Duration, amplitude and frequency of epileptiform events induced by 15 mM PTZ. ASD pharmacology |
| Hortopan et al., 2010 | Genetic (*mindbomb* mutant) | Deep | Fish immobilized in 1.2 % agarose. Extracellular LFP recordings in the forebrain and optic tectum. Field EPSP responses. Glass microelectrode (2−7 MΩ) filled with 2 M NaCl. | EEG characterization of the *mind bomb* mutant. Tectal field response to paired-pulse stimulation of the contralateral eye. Bursts frequency and duration. |
| Chege et al., 2012 | Genetic (KCNQ morphants) + pharmacological (Linopirdine-induced bursts) | Deep | Fish immobilized in 1.2 % agarose. Extracellular LFP recordings in the optic tectum. Glass microelectrode (2−7 MΩ) filled with 2 M NaCl. | Duration and frequency of spontaneous epileptiform events in (i) ATG-morphants and (ii) LPD-treated fish. |
| Afrikanova et al., 2013 | Pharmacological | Deep | Fish immobilized in 2% agarose. Extracellular LFP recordings in the optic tectum. Glass microelectrode (1−5 MΩ) filled with ACSF. | Pharmacological validation of the PTZ model. Number, mean duration and cumulative duration of epileptiform events (ictal and interictal). |
| Suls et al., 2013 | Genetic (*chd2* morphants) | Deep | Fish immobilized in 2% agarose. Extracellular LFP recordings in the optic tectum. Glass microelectrode (1−5 MΩ) filled with ACSF. | Occurrence of epileptiform events (no quantification). |
| Zdebik et al., 2013 | Genetic (*kcnj10a* morphants) | Surface | Fish paralyzed with D-tubocurarine and immobilized in 1.5 % agarose. Surface field potentials recorded on the skin above the optic tectum. Borosilicate glass microelectrodes filled with 1 M NaCl. | Occurrence of epileptiform events. Quantification of synchronous activities in the 2−4 Hz frequency band. Effect of ASDs on the power spectrum of paroxysmal events. |
| Schubert et al., 2014 | Genetic (*stx1b* morphants) | Deep | Fish immobilized in 2% agarose. Extracellular LFP recordings in the optic tectum. Glass microelectrode (2−10 MΩ) filled with ACSF. Hyperthermia: transient progressive elevation of the temperature of the microscope stage. Short-time Fourier transform for spectral analysis (time-frequency maps). | EEG characterization of the *stx1b* morphant. Mean and cumulative duration of polyspiking discharges and HFOs. EEG characterization of hyperthermic seizures. Spectral analysis: time-frequency maps and power spectral density of epileptiform events. |
| Galizia et al., 2015 | Genetic (*chd2* morphants) | Deep | Fish immobilized in 2% agarose. Extracellular LFP recordings in the optic tectum. Glass microelectrode (1−5 MΩ) filled with ACSF. Photosensitivity: dark/light switch (5 min dark, 5 min light recordings). | Characterization of epileptiform events induced by a sudden light exposure. Average, mean duration and cumulative duration of high frequency polyspiking activities. |
| Leclercq et al., 2015 | Pharmacological | Deep | Fish immobilized in 2% agarose. Extracellular LFP recordings in the optic tectum. Glass microelectrode (1−5 MΩ) filled with ACSF. | Pharmacological validation of the allylglycine model. Number, mean duration and cumulative duration of epileptiform events induced by allylglycine. ASD pharmacology. |
| Zhang et al., 2015 | Genetic (*scn1lab* morphants) + pharmacological testing | Deep | Fish immobilized in 2% agarose. Extracellular LFP recordings in the forebrain. Glass microelectrode (2−7 MΩ) filled with ACSF. | EEG and pharmacological characterization of the *scn1lab* morphant. Average, mean duration and cumulative duration of epileptiform events ASD pharmacological responsiveness. |
| Dinday et al., 2015 | Genetic | Deep | Fish paralyzed with α-bungarotoxine and immobilized in 1.2 % agarose. Extracellular LFP recordings in the forebrain. Glass microelectrode (2−7 MΩ) filled with 2 M NaCl. | Pharmacological screening in *scn1lab* mutants. Occurrence and number of epileptiform events after incubation. |
| Hong et al., 2016 | Genetic (*scn1lab* mutants) + pharmacological | Surface | Extracellular LFP recordings Multiple electrode arrays (electrode-integrated microfluidic system) | Characterization of PTZ-induced seizures, scoring. Electrograph and corresponding cross-correlation plots of seizures in response to two ASDs in *scn1lab* mutants. |

arborization defects, providing first-time evidence for the potential disease-modifying effects of fenfluramine. Interestingly, although the benzodiazepine diazepam decreased seizure number significantly in *scn1lab*$^{-/-}$ larvae, this drug was ineffective in rescuing the structural neuronal defects. BrdU staining indicated increased cell proliferation in *scn1lab*$^{-/-}$ larval brains, which was counteracted by chronic fenfluramine pretreatment.

In summary, these studies shed light on the early neuronal defects underlying Dravet syndrome. Altogether, behavioral and electrophysiological data obtained from both stable mutants as well as morphants confirm the relevance of the *scn1lab*$^{-/-}$ model in zebrafish as a model of Dravet syndrome.

#### 1.2.2. KCNJ10 and KCNQ3

Mutations in several potassium channel-coding genes have been associated with early onset epileptic syndromes such as benign familial neonatal seizures (BFNS), EAST/SeSAME syndrome or epileptic encephalopathies (Hahn and Neubauer, 2009; Maljevic and Lerche, 2014).

*KCNJ10* encodes the inward-rectifying potassium channel Kir4.1, expressed in glial cells (Olsen and Sontheimer, 2008). In patients, loss-of-function mutations of *KCNJ10* have been described in EAST/SeSAME syndrome, an autosomal recessive disorder consisting of epilepsy, ataxia, sensorineural deafness and renal tubulopathy (Bockenhauer et al., 2009; Cross et al., 2013; Scholl et al., 2009). Conditional knockout mice for *KCNJ10* die prematurely (postnatal day 20–25) and display stress-induced tonic-clonic seizures with jerking movements (clonic component) and stiffening of body and limbs (tonic component) (Bockenhauer et al., 2009; Djukic et al., 2007; Scholl et al., 2009).

In zebrafish, two studies have assessed the role of *KCNJ10* as a causative gene for EAST syndrome (Mahmood et al., 2013; Zdebik et al., 2013). The zebrafish orthologs *kcnj10a* and *kcnj10b* are expressed from 48 and 30 hpf, respectively (Mahmood et al., 2013). Selective MO-induced knockdown of *kcnj10b* leads to severe dysmorphology, preventing any behavioral or electrophysiological investigation. Knockdown of *kcnj10a* leads to movement defects characterized by an increase of spontaneous body contractions as early as 30 hpf. In 5 dpf larvae, posture and the swimming behavior elicited by the touch response test are also abnormal and could be interpreted as ataxia. Aberrant facial (jaw, eye) and fin movements can also be detected at that stage (Mahmood et al., 2013). Finally, paroxysmal locomotor activity is occasionally correlated with seizure-like activity consisting of a sudden burst of activity followed by a total loss of posture (Mahmood et al., 2013). Co-injection of the wild type human mRNA for *KCNJ10* could rescue these morphological and behavioral abnormalities, confirming that they result from *kcnj10a* knockdown. Co-injection of a mRNA containing the mutation associated with EAST syndrome in patients prevents such a rescue in morphants (Mahmood et al., 2013). The same two MOs were used by Zdebik et al. (2013) to evaluate the epileptic phenotype and EEG pattern of *kcnj10a* morphants. Electrical activity in the optic tectum was assessed with non-invasive surface glass electrodes, avoiding movement artifacts and trauma due to intracerebral pipettes commonly used to evaluate the electrical activity in agar-immobilized larvae. Five dpf *kcnj10a* morphants displayed paroxysmal events, occurring most of the time in clusters of spikes/poly-spikes, with a synchronized activity in the $2-4$ Hz frequency band (Zdebik et al., 2013). Interestingly, application of the anticonvulsant drug diazepam had no effect on seizure activity whereas pentobarbitone was able to prevent the occurrence of paroxysmal spiking events in this model (Zdebik et al., 2013).

The *KCNQ* gene family (KCNQ1-5) encodes $K_v7$ voltage-gated potassium channel subunits ($K_v7.1$-5), underlying the neuronal M-current that regulates excitability (Wang et al., 1998), with CNS-specific expression for KCNQ2-5. Mutations in the *KCNQ2* and *KCNQ3* genes have been associated with early-onset epileptic syndromes such as BFNS (Maljevic and Lerche, 2014) and more recently with severe epileptic encephalopathies (Epi4K Consortium et al., 2013; Orhan et al., 2014). Most of the mutations found in these patients are loss-of-function mutations, leading to a decreased seizure threshold. Nonetheless, a recent study found 4 different patients with gain-of-function mutations of *KCNQ2/3* genes, stabilizing the activated state of the channel and causing impairments in network interactions and hyperexcitability (Miceli et al., 2015).

In zebrafish larvae, $K_v7$ subunits 2, 3 and 5 (encoded by *kcnq2, kcnq3* and *kcnq5*) are widely expressed in the CNS with a stable expression of $K_v7.2$ and $K_v7.3$ from 2 to 7 dpf whereas $K_v7.5$ increases in a linear way from 3–7 dpf (Chege et al., 2012). In adult fish, $K_v7.2$ and $K_v7.3$ are mostly expressed in the brain and ear whereas $K_v7.5$ is mainly located in the ear (Wu et al., 2014). The involvement of $K_v7$ channels in epileptic disorders was confirmed in 3–7 dpf larvae. The selective blockade of $K_v7$ channels by linopirdine induces a significant increase of locomotor activity, with clonus-like convulsions at concentrations ranging from 50 to 100 μM (Chege et al., 2012). Such behavioral patterns are correlated with EEG discharges, occurring $1-1.5$ events/minute and lasting a few hundred milliseconds (Chege et al., 2012). The behavioral and EEG phenotype can be rescued by retigabine, a marketed ASD acting as potassium channel opener.

Finally, the functional knockdown of *kcnq3* by MOs in 3–5 dpf larvae (ATG-MO or splice-MO) reproduces the epileptic phenotype induced by linopirdine, with epileptiform discharges in about 70 % of morphants. Such spontaneous and recurrent events consist of poly-spiking discharges, occur every 3 min on average with a mean duration ranging from 300 to 400 msec (Chege et al., 2012).

#### 1.2.3. STX1B

The SNARE superfamily, including VAMP, SNAP25 and syntaxin 1A/1B proteins, is one of the most studied protein complexes responsible for synaptic vesicle priming, docking and fusion during neurotransmitter release (Bennett et al., 1992; Ramakrishnan et al., 2012). In the past decade, molecular components from the synaptic machinery have emerged as promising targets for antiepileptic drug development and several genes such as *SYN1* or *STXBP1* have been associated with rare genetic epileptic syndromes (Barcia et al., 2014; Carvill et al., 2014; Fassio et al., 2011).

*STX1B* encodes plasma membrane synaptic protein Syntaxin-1B and is primarily involved in exocytosis (Bennett et al., 1992). In rats, *STX1B* is expressed in cortical glutamatergic and GABAergic terminals and synapses (Bragina et al., 2010). In mice, *Stx1b* knockout leads to premature lethality from postnatal day 7–14, associated with severe motor dysfunction and brain malformations, underscoring a crucial role for *STX1B* in postnatal development and neuronal survival (Arancillo et al., 2013; Kofuji et al., 2014). Finally, *STX1B* was also shown to play a role in exocytosis and neuronal release efficiency by controlling the neurotransmitter pool size, refilling rate of priming vesicles and release probability (Arancillo et al., 2013; Mishima et al., 2014).

Whole genome and exome sequencing identified *STX1B* truncation and indel mutations in two large families with history of febrile seizures and early onset epilepsy. Further investigations in large cohorts of patients with fever-associated familial epilepsies or epileptic encephalopathies revealed one extra nonsense and two extra missense (Val216Glu and Gly226Arg) *STX1B* mutations (Schubert et al., 2014). A recent study by Vlaskamp and collaborators also described the involvement of *STX1B* in myoclonic astatic epilepsy in a 18-year old patient (Vlaskamp et al., 2016).

The human and zebrafish Stx1b protein sequences show 97 % identity. In zebrafish larvae, functional knockdown of *stx1b* was achieved with the use of two different MOs, mimicking loss-of-function by interfering with protein expression (Schubert et al., 2014). In this study, a 50 % reduction in Stx1b leads to abnormal behaviors and EEG events in 5-dpf larvae. Atypical behaviors are characterized by a lack of touch response (in 40 % of larvae), increased orofacial (jaw) and pectoral fin movements, as well as myoclonus-like jerks (Schubert et al., 2014) (see Tables 2 and 3).

The EEG correlate of these unexpected behaviors can be recorded spontaneously from the optic tectum, as a selective knockdown of *stx1b*

induces paroxysmal events in 45 % of 5 dpf morphants, whereas such activity is never present in control larvae. These events occur at a mean frequency of 12.9 ± 2.4 events/10 min with a mean duration of a hundred milliseconds. Paroxysmal EEG events consist of 2 main types of bursting activity: (1) polyspiking discharges, characterized by multispike activities with a power spectral density below 80 Hz and (2) high frequency oscillations (HFOs) defined by high voltage activities with a spectral component within the 100−200 Hz frequency band. Polyspiking discharges have a longer duration but occur less frequently than HFOs. Interestingly, a moderate increase in the temperature up to 31.5 °C induces seizures in both *stx1b* morphants and control larvae, but *stx1b* morphants are more sensitive to hyperthermia with a higher occurrence and duration of paroxysmal events compared to control larvae (Schubert et al., 2014). Co-injection of wild type human *STX1B* leads to the rescue of the epileptic phenotype, both in the ratio of larvae developing spontaneous EEG discharges, and in the number and cumulative duration of paroxysmal events (*stx1b* knockdown vs *stx1b* knockdown + wild type *STX1B*: 6.6 ± 0.8 vs 3 ± 1 events/10 min and 1582 ± 188 vs 656 ± 218 msec/10-min recording, respectively). Conversely, CNS-specific transgene expression of a mutated version of syntaxin-1B (human Val216Glu missense mutation) was unable to rescue the epileptic phenotype, with 21 out of 36 larvae displaying seizures in each group and no difference neither in the number of paroxysmal events nor the time spent in epileptic activity (Schubert et al., 2014). Together this indicates the observed phenotypes are due to *stx1b* knockdown, and not off-target MO effects.

Altogether, these data from both human and zebrafish studies suggest a causative role for *STX1B* in the pathophysiology of several epileptic syndromes, most probably with a loss-of-function mechanism (Schubert et al., 2014; Vlaskamp et al., 2016).

#### 1.2.4. STXBP1

Another member of the SNARE protein complex is STXBP1 (syntaxin-binding protein 1), which interacts with syntaxins 1, 2 and 3 in the brain (Pevsner et al., 1994) and coordinates SNARE complex assembly and membrane fusion (Dulubova et al., 2007). *STXBP1* mutations were discovered in children with early infantile epileptic encephalopathy (Saitsu et al., 2008) and were further diagnosed in patients suffering from Dravet syndrome as an example (Carvill et al., 2014). Additionally, *STXBP1* mutations were shown to contribute to comorbidities as disrupted sleep and metabolic circadian rhythms (Laakso et al., 1993) or neurodevelopmental delay (Saitsu et al., 2008).

In mice, a homozygous knockout model for *Stxbp1* is not viable while heterozygous mice are viable (Verhage et al., 2000). Toonen et al. (2006) have shown that if the expression of the protein is decreased, it results in a reduced synaptic vesicle release, which therefore impairs the efficacy of synaptic function. Behavioral experiments of heterozygous mice show increased anxiety and impaired emotional learning but no spatial learning deficit (Hager et al., 2014). Conversely, a mouse model that overexpressed *Stxbp1* specifically in the brain displayed several schizophrenia-related behaviors, hypersensitivity to hallucinogenic drugs and deficits in prepulse inhibition that reverse after antipsychotic treatment (Urigüen et al., 2013).

The zebrafish Stxbp1a and Stxbp1b amino acid sequences share 87.2 % and 78.5 % pairwise identity with human STXBP1 sequence, respectively, while the two zebrafish paralogs, Stxbp1a and Stxbp1b, share 74.9 % pairwise amino acid sequence identity (Grone et al., 2016). Using whole-mount colorimetric *in situ* hybridization, the authors determined that *stxbp1a* expression was prominent in all major CNS structures at early stages of the development while *stxbp1b* expression at 2 dpf and 3 dpf was more restricted to the olfactory bulb, the right habenula, and the outer regions of the retina. At a later stage, both *stxbp1a* and *stxbp1b* expression was also prominent in the telencephalon, optic tectum, cerebellar plate and medulla oblongata.

Using two stable mutant lines generated using CRISPR/CAS9 gene editing technology, the authors were able to demonstrate that zebrafish *stxbp1a* and *stxbp1b* have conserved roles in epilepsy and metabolic, physiological and behavioral development. When both genes are mutated, larvae at 5 dpf exhibit hyperpigmentation in the head and trunk/tail. However, only *stxbp1a* mutants show developmental morphological defects. LFP recordings revealed severe and spontaneous epileptic seizure events in *stxbp1b* homozygous mutant larvae, but not in *stxbp1a* homozygous mutant larvae. On the other hand, homozygous mutation of *stxbp1a* leads to physiological and behavioral deficits including immobility, reduced heart rate and metabolism (glycolysis and mitochondrial oxidative phosphorylation). The *stxbp1a*$^{-/-}$ mutants also exhibited premature death. This feature corresponds to the known phenotype of *Stxbp1*$^{-/-}$ mutant mice (Verhage et al., 2000). None of these physiological and behavioral deficits were observed in *stxbp1b*$^{-/-}$ mutant larvae. More severe neurodevelopmental phenotypes correlated with *stxbp1a* mutations may be related to its higher conservation and broader early CNS expression compared to *stxbp1b*.

#### 1.2.5. CACNA1A

P/Q calcium channels, highly expressed in the cerebellum and to a lesser extent, in the frontal cortex and CA1 region of the hippocampus, have a well-established role in neurostransmitter release. Mutations in *CACNA1A*, encoding the α1 subunit of P/Q calcium channels, have been implicated in 3 different autosomal-dominant diseases, namely, familial hemiplegic migraine type 1, spinocerebellar ataxia type 6 and episodic ataxia type 2 (Jen and Wan, 2018). It is believed that predominantly truncating mutations, mostly deletions or nonsense mutations, contribute to the occurrence of epilepsy. However, different types of seizures have been described in patients e.g. absence (Du et al., 2017), infantile epilepsy with myoclonus (Balck et al., 2017), febrile seizures (Choi et al., 2017; Lee et al., 2018) or early-onset epileptic encephalopathy (Damaj et al., 2015; Epi4K Consortium et al., 2013; Reinson et al., 2016). In addition, mutations in *CACNA1A* have been identified in humans suffering from absence seizures with or without cerebellar ataxia (Imbrici et al., 2004; Jouvenceau et al., 2001).

Recently, our group characterized for the first time, the *cacna1aa*-related phenotype in larval zebrafish (Gawel et al., 2020). In zebrafish, *cacna1a* is duplicated, sharing 72.01 % (*cacna1aa*) and 71.28 % (*cacna1ab*) homology with human *CACNA1A*. *in situ* hybridization analysis revealed that the *cacna1aa* paralog is highly expressed in the brains of 4- and 5-dpf larval zebrafish. Expression of *cacna1aa* was exceptionally high in the optic tectum and medulla oblongata of 5-dpf compared to 4-dpf larvae. Greater than 90 % knockdown of the *cacna1aa* paralog (using a combination of two antisense MOs), induced an epileptic phenotype both at the behavioral and EEG level. Phenotypically, *cacna1aa* morphants were slightly hyperpigmented, lacked a swim bladder, and had shorter body length compared to control-injected morphants. Four-day-old *cacna1aa* morphants were hypoactive in both the light and dark phases of the locomotor activity assay, compared to control MO-injected siblings. The EEG analysis revealed that 92 % of morphants exhibited epileptiform-like events, in the form of abrupt spike-wave complexes, polyspike-wave discharges and high-voltage spikes. Taking into account the pattern of behavioral changes, we predicted that the *cacna1aa*-related epileptic phenotype may be in fact absence seizures. To confirm our hypothesis, we analyzed the effect of 4 different drugs (sodium valproate, ethosuximide, lamotrigine and topiramate) and one contraindicated (carbamazepine) for the treatment of human absence seizures in our larval fish model. Indeed, pharmacological validation revealed that all 4 drugs, indicated for absence seizures in humans, significantly reduced the number of EEG discharges in *cacna1aa* morphants. However, ethosuximide and topiramate also decreased mean duration of EEG discharges. On the other hand, carbamazepine, which is contraindicated in patients suffering from absence seizures, did not affect the number and duration of EEG discharges in *cacna1aa* morphants. In summary, this is the first report providing evidence that *cacna1aa* knockdown in larval zebrafish induces an epileptic phenotype, which mimics aspects of human absence seizures. Thus, our model could prove useful for investigating *Cacna1aa*-mediated mechanisms of epileptogenesis and for high-throughput screening of new compounds.

#### 1.2.6. CHD2

More recently, genes not directly linked to ion conductance and/or synaptic transmission have been implicated in epileptic encephalopathies, such as chromodomain helicase DNA-binding protein 2 (CHD2). CHD2 is a member of SNF2-related superfamily of ATPases involved in chromatin remodeling and implicated in the regulation of gene expression, DNA-recombination and repair, cell-cycle regulation, development and differentiation (Harada et al., 2012; Marfella and Imbalzano, 2007; Shen et al., 2015). The protein structure of CHD2 consists of N-terminal tandem chromodomains, followed by a core SNF-like ATPase domain, and a c-terminal DNA binding domain (Liu et al., 2015). Whereas the core SNF-like ATPase domain catalyzes the ATP-dependent chromatin assembling, the N-and C-terminal accessory domains regulate both subtract specificity and chromatin remodeling activity of the core (Liu et al., 2015).

In humans, *de novo* mutations in *CHD2* are associated with a broad range of neurodevelopmental disorders, including intellectual disability, developmental delay, autism, and epilepsy phenotypes (Capelli et al., 2012; Chénier et al., 2014; Thomas et al., 2015). Individuals carrying the mutation frequently show diverse phenotypic presentations for a particular disorder (Carvill et al., 2013; Chénier et al., 2014). For instance, *CHD2* mutations were associated with different forms of epileptic encephalopathies, including Dravet syndrome (Suls et al., 2013), Lennox-Gaustat (Carvill et al., 2013; Lund et al., 2014) and myoclonic-atonic epilepsy (Carvill et al., 2013). However, in all cases, some distinctive epileptic-related features are observed, such as different age-of-onset, photosensitivity, and the occurrence of atonic-myoclonic absences (Carvill et al., 2013; Galizia et al., 2015; Suls et al., 2013; Thomas et al., 2015). Furthermore, these epileptic-related features are usually associated with intellectual disability and developmental delay (Carvill et al., 2013; Galizia et al., 2015; Suls et al., 2013; Thomas et al., 2015).

In the mouse embryo, *Chd2* is first expressed in the region that will form the heart, followed by forebrain and eye regions, and lately in ventral and dorsal sides of the embryo and extremities that will form the limbs (Kulkarni et al., 2008). *Chd2*$^{-/-}$ mutation that results in C-terminal truncation of the protein is lethal to mice, whereas the heterozygous mutation causes several developmental abnormalities, such as growth retardation, renal dysfunction, and lordokyphosis (Kulkarni et al., 2008; Marfella et al., 2008). Nevertheless, the occurrence of seizures was not described in these models (Kulkarni et al., 2008; Marfella et al., 2008). More recently, *Chd2* was shown to be expressed in a subset of neural progenitor cells during embryonic development of the cerebral cortex (Shen et al., 2015). By using a *Chd2* knockdown strategy in the brain through *in utero* electroporation, the same study concluded that Chd2 promotes the self-renewal of neural progenitor cells over their differentiation, since they observed increased neuronal differentiation in the cortical plate of the embryo cortex (Shen et al., 2015). By being involved in the development of the brain cortex, this study supports the contribution of *CHD2* gene mutations in the etiology of a broad spectrum of neurodevelopmental disorders including epilepsy.

The zebrafish Chd2 protein shares around 70 % identity with the human CHD2 protein. Suls and collaborators described developmental abnormalities triggered by partial *chd2* knockdown in zebrafish larvae via a splice site-targeting MO (Suls et al., 2013). From 2 dpf, morphants displayed pericardial edema, microcephaly, body curvature, absent swim bladder and stunted growth (Suls et al., 2013). At 4 dpf, behavioral abnormalities suggestive of epileptic seizures were also observed, such as burst activity (whirlpool-like events), pectoral fin and jaw twitching, and whole-body trembling (Suls et al., 2013). The presence of epileptiform discharges in these larvae were confirmed by LFP, which were absent in both wild type and larvae injected with a control MO (Suls et al., 2013). The epileptic discharges observed in *chd2* morphants consisted of multiple upward spikes of higher magnitude as compared to the control condition, and occasionally showing patterns similar to ictal-like events (Suls et al., 2013). In a more recent paper from Galizia and collaborators, the authors quantified the duration and number of discharges, cumulative duration in spiking activity and cumulative discharge frequency distribution of *chd2* morphants (as opposed to wild type) during a state of darkness followed by a period of light exposure (Galizia et al., 2015). Once more, the *chd2* morphants larvae showed higher frequency of discharges with longer duration as compared to controls (Galizia et al., 2015). Interestingly, the frequency and cumulative duration of discharges were higher during exposure to bright light as compared to a preceded period of darkness in *chd2* MO-injected larvae, but not in controls. The data support the evidence that *CHD2* mutations are associated with photosensitivity-induced seizures in humans, described in the same study (Galizia et al., 2015).

In summary, the *chd2* knockdown in zebrafish recapitulates some of the developmental abnormalities observed in rodents and the epileptic phenotype described in humans, and therefore represents a valuable model for the investigation of the mechanisms by which *CHD2* mutations are associated with epilepsy and for the screening of compounds with antiepileptic activity.

#### 1.2.7. LGI1

*LGI1* (Leucine-rich, Glioma-Inactivated 1) encodes a secreted protein involved in protein-protein interactions (Cowell, 2014; Kobe and Kajava, 2001; Somerville et al., 2000; Staub et al., 2002). Ottman et al. (1995) first described *LGI1* as responsible for a rare and hereditary epileptic syndrome defined as autosomal dominant partial epilepsy with auditory auras (ADPEAF, or ADLTE for autosomal dominant lateral temporal lobe epilepsy). More than 30 mutations have been described to date (Ho et al., 2012; Ottman et al., 2004), with about 50 % of ADPEAF-diagnosed patients carrying *LGI1* mutation and *de novo* mutations present in 2% of sporadic cases with lateral temporal epilepsy (Nobile et al., 2009). ADPEAF/ADLTE usually begins in the late adolescence (Michelucci et al., 2012; Nobile et al., 2009), is characterized by focal seizures with lateral temporal onset, associated in 70 % of cases with acoustic auras (Kalachikov et al., 2002; Michelucci et al., 2012). The evolution is most of the time benign with a good responsiveness to antiseizure therapy (Michelucci et al., 2003).

Most *LGI1* mutations are presumably haplo-insufficient and lead to the non-secretion of the protein, resulting in a loss-of-function (Kegel et al., 2013; Nobile et al., 2009). LGI1 is expressed in the CNS, predominantly in cortical and limbic neurons (Kalachikov et al., 2002; Senechal et al., 2005) and has been originally described as a tumor suppressor protein (Cowell, 2014; Gu et al., 2005a) prior to its potential involvement in both synaptic transmission (Fukata et al., 2010; Schulte et al., 2006) and neural development (Owuor et al., 2009; Zhou et al., 2012, 2009).

*Lgi1*$^{-/-}$ mice develop early onset spontaneous seizures and die prematurely (by postnatal day 21). Generalized seizures are characterized by a behavioral arrest followed by erratic jumping/running and stereotypic clonic and tonic movements of the limbs (Chabrol et al., 2010; Fukata et al., 2010; Yu et al., 2010). EEG discharges were found to originate from the hippocampus rather than cortical structures (Chabrol et al., 2010). Interestingly, *Lgi1*$^{+/-}$ mice never show this seizure phenotype (Chabrol et al., 2010; Fukata et al., 2010; Yu et al., 2010) but are more sensitive to audiogenic (Chabrol et al., 2010) and PTZ-induced seizures (Fukata et al., 2010). Finally, Boillot et al. (2014) and collaborators recently showed that Lgi1 deficiency restricted to glutamatergic neurons is sufficient to induce spontaneous seizures in *Lgi1*$^{-/-}$ mice.

In zebrafish, *lgi1a* and *lgi1b* share the same structure as the mammalian *LGI1* gene (Gu et al., 2005a, b). Early in development, both genes are highly expressed in the optic tectum. Additionally, *lgi1a* is expressed in the ventral parts of the mid- and hindbrain, while *lgi1b* is more dorsally expressed in these structures, as well as in the cerebellum (Gu et al., 2005a, b).

*lgi1a* knockdown by splice MO (90 % knockdown at 72 hpf) induces developmental abnormalities such as reduced brain and eye size with increased apoptosis, heart edema and tail abnormalities (Teng et al., 2010). More importantly, these larvae display epileptic-like behaviors such as hyperactivity characterized by whirlpool swimming and myoclonic-like jerks, similar to seizure stage I-II described in PTZ treated larvae (Baraban et al., 2005; Teng et al., 2010). Interestingly, the use of a translation blocking MO at the same concentration leads to a significant increase in the death rate whereas lower doses are unable to induce any paroxysmal behavior or

morphological impairment (Teng et al., 2010).

Reduction of *lgi1b* (80 % knockdown at 72 hpf by splice MO) leads to severe and long lasting developmental abnormalities, mainly represented by hydrocephalus, eye and brain malformations, heart edema and body curvature but no overt epileptic phenotype (Teng et al., 2011), suggesting a more important role in normal brain development rather than epilepsy. Both *lgi1a* and *lgi1b* knockdown-induced phenotypes can be rescued by co-injection of mRNA, with a significant reduction of abnormal behaviors and morphological/histological alterations (Teng et al., 2011, 2010).

Finally, synergy studies have shown that a partial loss-of-function of either *lgi1a* or *lgi1b* does not induce any epileptic phenotype but increases the sensitivity to proconvulsant entities such as PTZ (Teng et al., 2011, 2010). Both *lgi1a* and *lgi1b* morphants incubated with low dose PTZ (2.5 mM) display hyperactivity characterized by increased movement and erratic swimming whereas 3 dpf control or uninjected larvae only show a moderate increase in swimming (Teng et al., 2011, 2010).

In summary, *lgi1a* and *lgi1b* seem to play distinct roles in seizure activity in zebrafish, with *lgi1a* more directly involved in epileptiform-like activities whereas *lgi1b* could have a modifying effect on seizures (Cowell, 2014; Teng et al., 2011, 2010).

#### 1.2.8. GABRA1A

*GABRA1A* encodes the α1 subunit of $GABA_A$ receptor and in human mutations in this gene have been shown to cause both mild to severe generalized epilepsies (Carvill et al., 2014; Cossette et al., 2002; Hirose, 2014). Deletion of the $GABA_A$ receptor α1 subunit in mice resulted in the loss of 50 % of all these receptors in the brain (Kralic et al., 2002), but knockout mice exhibited only tremors, and no epileptic phenotype (Kralic et al., 2005), suggesting *GABRA1A* deficient rodent models do not recapitulate all the symptoms of the human condition.

Recently, Samarut et al. (2018), using CRISPR/Cas9-mediated gene editing, generated a new *gabra1*$^{-/-}$ mutant zebrafish line in order to unravel the epileptogenic mechanisms underlying *gabra1* deficiency. Zebrafish have a single ortholog, *gabra1a*, with 83 % homology with the human protein. Wholemount *in situ* hybridization analysis revealed that *gabra1a* transcripts were highly expressed in the CNS and spinal cord, beginning at 18 hpf and reaching a peak at 48 hpf. *gabra1*$^{-/-}$ mutants developed normally but died prematurely between 7 and 10 weeks of age. Interestingly, both larval and juvenile fish exhibited an epileptic phenotype, i.e. upon exposure to light they displayed fully penetrant tonic-clonic-like seizures, which were abolished by prior exposure to valproic acid, clonazepam or levetiracetam, while carbamazepine had only a mild effect (Samarut et al., 2018).

Additionally, while brain structure and neuronal populations in *gabra1*$^{-/-}$ larvae were not affected, RNA sequencing revealed down-regulation of genes involved in axon guidance or GABAergic synapse function and trafficking, as well as genes encoding GABA receptor subunits (other than $GABA_A$). The analysis of Gad1/2-containing structures in mutant brains indicated a decrease in Gad1/2-labelled neurofilaments, pointing to a reduction in GABAergic presynaptic signaling. This was accompanied by a decrease in expression of gephyrin-positive clusters in mutant brains (i.e. the marker that anchors the postsynaptic GABA receptors to the cytoskeleton). In summary, this comprehensive study clearly showed that *gabra1* is not mandatory for the development of the GABA neuronal population but is required for the proper wiring of this inhibitory synaptic network, underlying the *gabra1a* epilepsy phenotype (Samarut et al., 2018). Moreover, it highlighted that new therapeutic strategies should be focused on restoring neurodevelopmental defects at early stages, rather than treating them symptomatically later on. Finally, this study confirmed the potential of zebrafish for elucidating mechanisms underlying epileptogenesis.

#### 1.2.9. DEPDC5

In 2013, a mutation in *DEPDC5* (DEP domain containing protein 5) was first reported in autosomal-dominant familial focal epilepsy (Dibbens et al., 2013; Ishida et al., 2013). Since then, mutations in *DEPDC5* have been identified in 12–37 % of all cases of focal epilepsies, predominantly causing premature codon termination (Baulac et al., 2015; D'Gama et al., 2017; Picard et al., 2014; Scerri et al., 2015). Using lymphoblastoid cell lines obtained from three patients with different nonsense mutations, it was recognized that the focal epilepsy phenotype is related to *DEPDC5* haploinsufficiency (Ishida et al., 2013; Picard et al., 2014).

*DEPDC5* encodes a protein which is a member of GATOR1 (Gap Activity Towards Rags) complex, being a negative regulator of mTORC1 (mechanistic target of rapamycin complex 1) (Bar-Peled et al., 2013; Marsan and Baulac, 2018). Hyperactivation of mTORC1 has been suggested to play a key role in epilepsy syndromes (Crino, 2016; de Calbiac et al., 2018). Rodent knockout models of *Depdc5* deficiency revealed the key role of this gene in embryonic development, since null mutations resulted in embryonic lethality (Hughes et al., 2017; Marsan et al., 2016). Surprisingly, *Depdc5*$^{+/-}$ mice exhibited mTORC1 hyperactivation, severe morphological abnormalities, but spontaneous seizures were not observed in these animals (Hughes et al., 2017; Marsan et al., 2016).

In zebrafish, there is only one ortholog of *DEPDC5,* sharing a 75 % amino acid identity with the human gene. de Calbiac et al. (2018) reported the first knockdown of *depdc5* in zebrafish, induced by splice- and translation blocking MOs. In this study, authors found that loss-of-function of *depdc5* led to motor hyperactivity of embryos as early as 17 hpf (tail flicks, coils, recurrent tremors). At 48 dpf, *depdc5* morphants exhibited an aberrant locomotion pattern, but not an overall locomotion impairment. Co-expression of human *DEPDC5* in morphants rescued the hyperactivity phenotype, while injections of mutant human *DEPDC5* cDNA (containing two different mutations described in focal epilepsy patients, i.e. p.Arg487* and p.Arg485Gln) did not. Lastly, chronic treatment of *depdc5* morphants with rapamycin, a negative modulator of mTORC1, significantly ameliorated the motor disturbances in morphants (de Calbiac et al., 2018).

Using CRISPR/Cas9, Swaminathan et al. (2018) designed another model of *depdc5* deficiency in zebrafish, in which targeting of exon 14 of this gene led to expression of a truncated protein and, in consequence, loss-of-function of *depdc5*. *depdc5*$^{-/-}$ larvae did not possess any gross morphological defects, but they were smaller in body length as compared to *depdc5*$^{+/+}$ larvae and died by 2 weeks of age. Furthermore, hyperactivation of the mTOR pathway in homozygous larvae was indicated by increased phosphorylation of ribosomal protein S6 (pS6; readout of mTOR hyperactivation), and in 21 % of *depdc5*$^{-/-}$ larvae, spontaneous EEG discharges were detected. Although mutants were hypoactive, acute exposure to a low concentration of PTZ (3 mM) induced a significant increase in their locomotor response in comparison to control larvae. RNA sequencing of mutant brains revealed the changes in the expression level of numerous different genes, e.g. those responsible for aminoacyl-tRNA biosynthesis, morphogenesis, axonogenesis, synapse formation or GABA-mediated signaling. With regard to GABA-related genes, immunostaining with Gad1/2 revealed reduced number of Gad1/2 projections in *depdc5*$^{-/-}$ larvae. Since GABA receptor agonists could not rescue the *depdc5*$^{-/-}$ larval phenotype, while vigabatrin (preventing GABA breakdown) was able to do this at least in part, the authors concluded that the compensating effect of GABA is more likely to be caused by the effect of GABA *per se* rather than through GABA receptors. This comprehensive study pointed toward a novel mTOR-independent effect of *depdc5* deficiency on GABA-mediated signaling, which in turn, may underlie focal epilepsy pathogenesis (Swaminathan et al., 2018).

#### 1.2.10. UBE3A

Notch signaling has been recognized to play an essential role in early brain development (Chitnis et al., 1995; de la Pompa et al., 1997). Recently, E3 ligases were found to modulate Notch signaling by ubiquitin-dependent protein degradation and endocytosis (Lai, 2002). In mice, a null mutation of *Ube3a* causes impairment of long-term potentiation, increases seizure susceptibility and, in some of animals, bursts of spike-wave discharges (Jiang et al., 1998; Miura et al., 2002).

Lu et al. (2009), reported deficits in dendritic arborization of sensory neurons in *Drosophila UBE3A*$^{-/-}$ mutants. In humans, mutations or small deletions leading to *UBE3A* loss-of-function resulted in excessive differentiation of early-born cell into neurons, and were found to be linked with autism (Glessner et al., 2009) and/or Angelman syndrome (Camprubí et al., 2009; Clayton-Smith and Laan, 2003; Kishino et al., 1997). In humans, Angelman syndrome is characterized by motor dysfunction, developmental delay, intellectual disability, learning disability, absent speech, abnormal sleep pattern and severe seizures (Buiting et al., 2016). Currently, the only medical strategy for the treatment of Angelman syndrome is symptomatic (Buiting et al., 2016).

Mutagenesis screens in zebrafish identified several mutants of the Notch signaling pathway (Hortopan et al., 2010; Itoh et al., 2003; Schier et al., 1996). For one of these mutants, *mib*$^{hi904}$, Hortopan et al. (2010) reported spontaneous multi-spike bursts, similar to prolonged ictal-like discharges, in 93 % of mutants at 3 dpf, via EEG recordings from the optic tectum or forebrain. Next, the authors performed transcriptomic analysis, identifying significant upregulation of brain-derived neurotrophic factor (BDNF) gene (*bdnf)* and peptide YYa (*pyy*, member of neuropeptide Y family). On the other hand, expression of *gad1, gabra1* and *glra4b* (α4 glycine receptor subunit, mediating inhibitory neurotransmission) was strikingly reduced in *mib*$^{hi904}$ mutants. As follow-up of this study, Hortopan and Baraban (2011) investigated genes related to Notch signaling and neurodevelopment. A thorough expression analysis of 9 of these genes (*her4.2, hes5, bhlhb5, hoxa5a, hoxb5b, dmbx1a, dbx1a, nxph1, and plxnd1)* revealed a prominent downregulation for most of them, especially in the pallium, ventral thalamus and optic tectum. In summary, these two studies gave insight into the mechanisms underlying the epileptic phenotype in Angelman syndrome (reduced GABA-mediated signaling pathway) and abnormalities in brain development related to Notch signaling (Hortopan et al., 2010; Hortopan and Baraban, 2011) (see Table 3).

### 1.2.11. ALDH7A1 and PLPBP

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive genetic syndrome with recurrent and intractable neonatal or infantile seizures as a core symptom (Baxter, 1999; Gospe, 1993). If untreated, PDE may progress to SE, often resulting in death. To date, only high doses of vitamin B6 (pyridoxine), or PTP coupled with arginine adjunct supplementation and a lysine-restricted diet, are considered to be therapeutic treatment options in human patients, preventing seizure occurrence and other long-term metabolic consequences (Coughlin et al., 2015; Stockler et al., 2011; van Karnebeek et al., 2014). *ALDH7A1* (also named antiquitin) encodes the enzyme α-aminoadipic-semialdehyde-dehydrogenase, which is responsible for lysine catabolism. Pathogenic mutations of *ALDH7A1,* leading to loss-of-function of this gene, cause the accumulation of lysine metabolites aminoadipate semialdehyde (AASA) and piperideine-6-carboxylate (P6C) in CNS and other tissues. However, the pathophysiology of PDE remains very poorly understood.

Two groups almost simultaneously reported the first animal models of PDE-dependent epilepsy (Pena et al., 2017; Zabinyakov et al., 2017). Mutant *aldh7a1*-knockout lines were generated by CRISPR/Cas9, and the observed changes were similar in both models. Homozygous larvae did not survive beyond 14 dpf. Morphologically, *aldh7a1*$^{-/-}$ mutants were indistinguishable from heterozygous and wild type siblings until 10 dpf but displayed a curved body axis at later stages. *aldh7a1*$^{-/-}$ mutants exhibited hyperactive behavior with rapid circling swimming and body convulsions, starting at 10 dpf and progressing with time. Interestingly, this hyperactivation was induced immediately upon light stimulus, although some sporadic convulsions were also detected in darkness (Pena et al., 2017). Changes in behavior of *aldh7a1*$^{-/-}$ mutants were accompanied by high amplitude ictal- and low amplitude inter-ictal-like EEG discharges (Pena et al., 2017; Zabinyakov et al., 2017). Additionally, chronic incubation of larvae with pyridoxine (Pena et al., 2017) or PLP substantially prolonged the life span of *aldh7a1*$^{-/-}$ mutants, with pyridoxine being more effective. This was accompanied by a decrease in the number and duration of EEG discharges, which returned to baseline 2–6 days after the treatment was discontinued (Pena et al., 2017), which is in agreement with human findings (Schmitt et al., 2010). Pyridoxine responsiveness of *aldh7a1*$^{-/-}$ mutants was also evidenced by decreased *c-fos* expression, as compared to untreated mutants (Pena et al., 2017).

To give further insight into pyridoxine-dependent pathology, *aldh7a1*$^{-/-}$ mutants were treated with lysine before the onset of seizures, which resulted in death within 48 h upon exposure to lysine (Pena et al., 2017). Additional experiments indicated that the observed seizure phenotype is associated with pyridoxine deficiency, rather than the effect of AASA and P6C accumulation or nonlysine-related *aldh7a1*$^{-/-}$ loss-of-function. Next, using LC-MS-MS, analysis of different metabolites of 11 dpf larvae was done, revealing changes in the level of 11 metabolites and neurotransmitters. Among them, levels of GABA and PLP were lower, while levels of e.g. AASA and P6C were higher (Pena et al., 2017; Zabinyakov et al., 2017). Taking into account that PLP is a cofactor necessary for GAD activity, this may at least partially explain the mechanisms underlying PDE-dependent seizure pathogenesis (Pena et al., 2017). Due to the limited number of therapeutic options for PDE patients, utilization of this model for high-throughput screening of compounds may contribute to proposal of new treatment regimens.

A new gene which has been recently implicated in vitamin B6-responsive disorders is *PLPBP,* encoding PLP homeostasis protein (Darin et al., 2016; Plecko et al., 2017). Patients with PLPBP deficiency, as a result of loss-of-function mutations of this gene, exhibit severe early-onset seizures that are uniquely responsive to pyridoxine or PLP (Darin et al., 2016). Recently, Johnstone et al. (2019) has reported a cohort of 12 patients with biallelic mutations in *PLPBP*. Using a zebrafish model of PLPHP deficiency, this group sought to analyze, at least partially, the underlying pathology of PLPBP deficiency. *plpbp*$^{-/-}$ mutants died by 16 dpf, and exhibited spontaneous seizures starting at 10 dpf. They were responsive to pyridoxine treatment, and to a lesser extent, PLP. Chronic treatment with pyridoxine substantially increased their life span, decreased hyperlocomotion and reduced the number of epileptiform-like events. Furthermore, analysis of metabolites in the brains of 10 dpf *plpbp*$^{-/-}$ mutants revealed a disruption of GABA, catecholamine and amino acid levels, suggestive of an impairment of PLP-dependent enzymatic pathways. In summary, this model recapitulates the human PLPHP deficiency phenotype and may serve as a screening platform for drug discovery.

### 1.2.12. TSC2

Tuberous sclerosis complex (TSC) is a rare genetic syndrome caused by loss-of-function mutations in *TSC1* or *TSC2*, encoding hamartin and tuberin, respectively. The genes are classified as tumor suppressor genes, and via indirect mechanisms negatively regulate the mTOR pathway (Huang and Manning, 2008; Qin et al., 2016). Patients suffering from TSC exhibit diverse renal, cardiac, dermatological or ophthalmic symptoms. Neurological and neuropsychiatric symptoms include autism, intellectual disability and epilepsy, the latter being the most commonly observed comorbidity in TSC patients (Crino, 2016; Curatolo et al., 2015). Focal seizures and infantile spasms usually occur in the first year of life and remains refractory to treatment (Jeong et al., 2017). Currently, vigabatrin, being a modulator of both GABA and mTOR pathways, is considered to be a drug of choice for TSC patients (Curatolo et al., 2015; Zhang et al., 2013). Still, there is a high need for other therapeutic options, and zebrafish models have opened a new route for TSC drug discovery.

While the first study of aberrant *tsc* expression in zebrafish focused more on its role in brain malformations (Kim et al., 2011), it was Scheldeman et al. (2017) who first analyzed this mutant line with regard to TSC-associated epilepsy. Morphologically, *tsc*$^{-/-}$ mutants did not exhibit gross malformations, with the exception of non-inflation of their swim bladders. The touch response of mutants was not disturbed, but mutants died by 11 dpf. Immunohistochemical analysis of *tsc*$^{-/-}$ larval brains revealed an increase in phosphorylated protein S6 (pS6) level, a readout of mTOR hyperactivation. Additionally, mutants had larger brains compared to wild type and *tsc*$^{+/-}$ siblings. Behaviorally, *tsc*$^{-/-}$ mutants did not differ in locomotor activity from wild type and *tsc*$^{+/-}$ siblings when this assay was

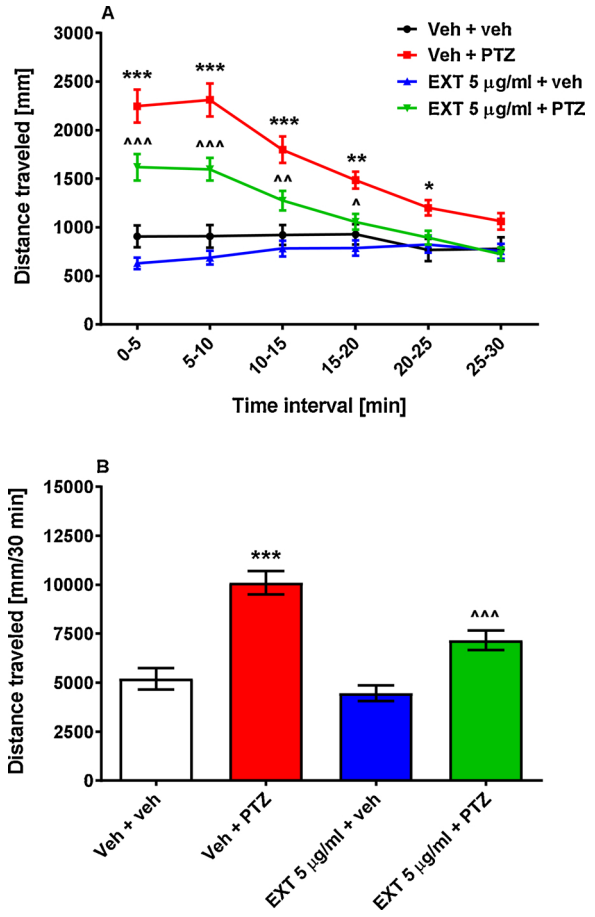


**Fig. 3.** Example of a zebrafish behavioral assay showing anticonvulsant activity of a plant extract used in Kazakhstan. Zebrafish larvae were pretreated with the ethanolic plant extract (5 μg/mL) for 20 h before acute exposure to pentylenetetrazole (20 mM). Pentylenetetrazole-induced hyperlocomotion was measured 5 min after exposure, using an automated video-tracking device. Graph shows total distance traveled by larvae in millimeters per 5-min interval during a 30-min tracking session (A) and total distance traveled within 30 min (B). Data were analyzed using two-way with/without repeated-measures ANOVA, followed by Tukey's or Bonferroni's *post hoc* test (n = 30-32/group). $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$ (vs Veh + veh) $^{\sim\sim}p < 0.001$, $^{\wedge\wedge}p < 0.01$, $^{\wedge}p < 0.05$ (vs Veh + PTZ). EXT- extract; PTZ- pentylenetetrazole; Veh- vehicle.

conducted in the light. However, in the dark *tsc*$^{-/-}$ mutants were hypoactive. Moreover, 54 % of mutant larvae displayed EEG discharges, with average number of 4 seizures per 10 min recording. RNA sequencing analysis of gene expression in *tsc*$^{-/-}$ larval brains indicated the activation of mTOR pathway in *tsc*$^{-/-}$ mutants, as well as upregulation of genes related to inflammation, immune responses and downregulation of calcium channels. Pharmacological inhibition of mTOR with rapamycin in *tsc*$^{-/-}$ mutants revealed an increase in survival rate, a rescue of reduced locomotor activity and a decrease in pS6 level. As a follow-up of this study, Serra et al. (2019) sought to determine the influence of cannabidiol (CBD), the main cannabinoid derived from *Cannabis sativa*, on the epilepsy phenotype in *tsc*$^{-/-}$ larvae. CBD treatment from 3- to 7-dpf affected neither locomotor activity nor survival rate of homozygotes, but strikingly reduced the number of pS6-positive cells and their cross-sectional size. In summary, the obtained data suggest that CBD modulates the mTOR pathway by inhibition of its activity. Although the relevance of this results seems to be promising, further studies are warranted to determine if CBD may be used in the therapeutic management of TSC patients.

## 2. Conclusion

Here, we have made a summary of currently available zebrafish epilepsy models. With their high fecundity, rapid development and relatively low maintenance costs, in addition to their ability to take up compounds from the water surrounding them, zebrafish are particularly suited to perform drug screens.

Depending on the aim of the research, different genetic or chemical models are available. Both in zebrafish and rodent models, PTZ is by far the most characterized chemical model. It acts on $GABA_A$ receptors and depending on the concentration applied, induces seizure-like behavior and epileptiform discharges over longer or shorter time periods in larval zebrafish. Therefore, when using locomotor activity as a readout for ASD activity, one should consider not only cumulative distance travelled over time, but also the kinetics of locomotion over several time intervals, in order to maximize the knowledge gained from such experiments. Other chemical compounds are available to induce discharges, such as AG, EKP and kainate, though these are less commonly used and warrant further characterization before application in large-scale drug screens. However, as these compounds act through distinct pathways to induce seizures, the efficacy of potential ASDs in a broader set of models would be of interest.

In addition to carrying out drug discovery screens in a broader set of pharmacological models, specific genetic models are also worth investigation. Stable genetic models are available for Dravet syndrome, rare syndromes associated with synaptic vesicle transport, *GABRA1A*-related generalized epilepsies, epilepsy linked to Angelman syndrome, *DEPDC5*-related focal seizures, PDE and TSC. Furthermore, transient models using antisense MO knockdown have been reported for EAST/SeSAME, Lennox-Gastaut, and ADPEAF/ADLTE. Such models may be valuable in the identification of potential ASDs for patients that currently have no satisfactory medication strategy available to them.

Possible mechanisms of epilepsy onset and the effects of pharmacological intervention therein can be investigated through high-resolution spatial and temporal imaging. In order to test potential ASDs in a high-throughput manner, locomotor activity assessment is most suited for initial drug screens. Any hits from such screens can subsequently be assessed for their seizure inhibitory effect using LFP recordings from larval brains, before undergoing further validation, such as in rodent models.

## Ethical statement

Zebrafish experiments (Fig. 3) were approved through the Norwegian Food Safety Authority experimental animal administration's supervisory and application system ("Forsøksdyrforvatningentilsynsogsøknadssystem"; FOTS 18/106800-1).

## Authors's contributions

All authors participated in the writing of the manuscript. KG and WE prepared the figures. ADC and CVE conceptualized the content and scope of the article. KG, WE and CVE proofread and edited the final draft.

## Declaration of Competing Interest

Nothing to declare.

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