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Zebrafish as a New Platform Used in Exploration of Ketamine-Induced Neurodevelopmental Toxicity

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Abstract

We have modified the abstract as 'Previous studies have already found out that commonly used anesthetic, ketamine, has toxic effects on neurodevelopment. Unlike most rodent models just focusing on neuronal apoptosis caused by ketamine, early stages of neuron development abnormality in zebrafish can be assessed in vivo because of the transparent embryos and larve. And also thanks to its cost-efficiency and quick reproduction, large-scale behavior analyses and gene screens can be conducted in zebrafish. Besides, the whole genome of zebrafish has already been sequenced and its gene functions are highly conserved during evolution, which makes the experiments more reliable on zebrafish model. So Zebrafish has obvious advantages in the researches of ketamine neurotoxicity over the conventional animal models (such as mice). Within this paper we illuminate how we can use this model to study ketamine neurotoxicity. In the future, along with more advanced genetic technologies joining this platform will not only make up for conventional models to deeply understand neurodevelopmental toxicity of ketamine, but also might provide the unique insight to the field of neurodevelopment and neurotoxicity impaired by other drugs

Keywords: Zebrafish; Ketamine; Neurodevelopmental; Toxicity

Introduction

Ketamine, a noncompetitive NMDA glutamate antagonist, has been widely used as a pediatric anesthetic for procedural sedation and pain relief [1-5]. In the meantime, an increasing number of both clinical and lab researches focus on developmental neurotoxicity of ketamine since an article published on Science, which first reported that blockade of NMDA receptor will produce neurotoxity in the developing rat brains [6].

Large numbers of studies with conventional animal models have revealed that ketamine can cause neuronal apoptosis during the critical period of the developing brain [7-12]. Also a preliminary clinical study indicated that exposure to ketamine over 3 times was detrimental to neurodevelopment in infants [13]. So further investigations become truly significant, which will elucidate how ketamine does harm to the developing neural system.

However, the neurodevelopment of traditional animals cannot be observed directly in vivo due to in-utero embryogenesis of these creatures. Under this condition, zebrafish emerged as a powerful weapon to solve out this puzzle. Henceforth we can effectively and intuitively evaluate the toxicity of ketamine imposing on the neurodevelopment in real time.

First of all, zebrafish develops outside the utero during embryonic period and maintains transparent until most organs become mature [14-16]. Given that we utilize the transgenic zebrafish as live biosensors to test the side effects of ketamine, whose specific regions can be labeled by some visible proteins (GFP) [17-20]. Secondly, short mature period and generous reproduction make it more suitable for high-throughput screening than mice [21]. Thirdly, NMDA receptors are primary targets of ketamine whose subunit, NR1, owns the highly conserved sequence across zebrafish and humans. Zebrafish genome also contains paralogs for the rest of NMDA receptor subunits in humans. Moreover previous studies demonstrated that ketamine toxicity is somehow related to up-regulated NR1 expression in rodent models. Simultaneously, among the 10 NMDA subunits that zebrafish possesses, there're two of them expressed during embryonic time [7,10,12,22-24]. That means experimental results coming out of zebrafish could extrapolate to humans and also could explain some phenomenon highly conserved in evolution [23]. All the above indicate that it is rational and potent to study neurodevelopmental toxicity of ketamine via this new animal model.

To elucidate the characteristics of these two animal platforms more directly, we briefly integrate and summarize them in Table 1, which are mentioned in these articles [25-27].

	Advantages	Disadvantages
Zebra fish	1.Comparison to the human reference genome shows that approximately 70% of human genes have at least one obvious zebrafish orthologue	Poor water soluble drugs and compounds cannot be well administered by zerbrafish
	2. Zebrafish has abundant and quick reproduction abilityshort experimental cycle and cost less for high-throughput screening of candidate genes and small molecular compounds	2. Behavior phenotypes are less sophisticated than mammalians;
	3. Zebrafish's nervous structure remains the typical complexity of	3. Some structures in nervous system of mammalians cannot

	vertebrate systems but relatively simple enough to precisely analyses the pathophysiologic mechanism conserved during evolution	find counterparts in zebrafish with similar functions;
	4. With over 1000 transgenic and mutant zebrafish strains for researchers to choose according to different neurologic disease modelsand with abroad genetic tools of zebrafish	
Mice	1. Mouse is the most broadly used animal tool for preclinical trials and has 90% genetic homology with human race.	1. We cannot get visual of abnormality of mouse fetus when it happens in utero and it will be problematic to measure the exact concentration of drugs that impact mouse during embryonic period
	2.There are many practical genetic or molecular tools designed for researches and there are well quantified standard for mouse's behavioral study	2. High-throughput screening via mouse model will be time-consuming with low efficiency compared to zebrafish.
	3. Mouse models have already been successfully used to identify drug targets and to provide efficacious and safe dosage regimens for combination treatments in humans	3. It is unlikely to accurately interpret how nervous circuit works in mouse brain.

Table 1: As shown in the table above zebrafish is capable of sufficiently making up for the traditional animal model. Furthermore cross-species comparison implied a common basis for mechanism relevant with abnormal neurodevelopment. In that case lab work will serve the subsequent clinical more objectively.

Physical damage of ketamine in zebrafish's nervous system

Present studies about physical damages caused by ketamine have shown that we can either conclude it from apoptosis staining or count the survived neuron number with the help of specific-neuron-targeted green fluorescent protein. Besides, the particular gene expression level can give us a hypothesis that how a specific signaling pathway involved in physical damage after ketamine exposure. Both higher and lower concentrations of ketamine mentioned below are sub-anesthetic doses [28].

Ketamine exposure did not significantly increase the obvious malformations of nervous system in both survived embryonic and larval zebrafish. But after acridine orange (AO) staining, experimental groups, which were exposed to lower concentration of ketamine, showed no more cellular deaths than the control group [29-31]. However, exposure to higher concentration of ketamine will cause apoptosis in the region of thalamus and the connection part between midbrain and after brain. There are two possible explanations. On the one hand lower dosage ketamine only slow down the development or differentiation of neural cells and on the other hand neurons may have degenerated by a process other than apoptosis, likely, necrosis. Thus we cannot see any differences from apoptosis staining [31].

Motor and sensory neuron developments are more sensitive parameter of physical damages than apoptosis in zebrafish, which was never used in rodent models before. Hb9:green-fluorescent-protein(hb9:GFP) transgenic zebrafish, in which the promoter of the transcription factor hb9 that is found in developing motor neurons of zebrafish, drives GFP expression specific ally in motor neurons [17,18,20,29,31]. Some researchers found out that ketamine exposure resulted in a reduction in the GFP intensity in the motor neurons resided in the cranial and spinal area of zebrafish embryos. To be more specific, there was a significant reduction (30%) in the number of spinal motor neurons in ketamine-treated embryos [29,31]. And the axon length of motor neuron has an approximated 20% reduction compared to the control group. In embryos treated with ketamine plus acetyl L-carnitine, the number of spinal motor neurons was restored, almost to control levels, which suggests that ketamine's adverse effect on the motor neurons is prevented by acetyl L-carnitine [31].

Rohon beard neurons are the primary sensory neurons to develop along the neural axis and might be the first to suffer from toxicity of ketamine due to their superficial location beneath the skin of zebrafish embryos. An experiment conducted whole mount immunohistochemistry with a specific antibody to identify the RB neurons in zebrafish. Finally this experiment implicated ketamine is harmful to these sensory neurons as well. But in embryos treated with ketamine plus acetyl L-carnitine, ketamine's adverse effect is also prevented by co-treatment with acetyl L-carnitine [31,32].

To further investigate adverse effects of ketamine that induced a reduction in both motor neurons and sensory neurons, some group mainly detected the discrepancy on molecular level before and after ketamine exposure. The target gene picked up by researchers came from two isolated signaling pathways which are essential for motor neuron development and axonogenesis. One of them includes Notch1a (a gene that is necessary for neuron survival but inhibiting progenitor cells finishing neuronal commitment [33-35]), Ngn1 (a direct downstream gene of Notch inhibition [36,37]) NeuroD (a direct downstream gene of Ngn1 that is expressed in differentiated neurons [37,38]. This experimental result showed that ketamine down-regulated the expression of Notch 1a with the dramatic up-regulation of Ngn1expression. Nevertheless, NeuroD, downstream gene of Ngn1 remained repressed. Adding this together ketamine promotes the neural commitment but also triggers neurons degeneration or apoptosis via sustained inhibiting the expression of Notch1a. It explains why we get fewer neurons along with less expression of NeuroD at last. [29]

The other signaling pathway contains Gli2a and Gli2b genes, which are in charge of the development of some cellular lineages, such as the ventral neural precursors, cranial motor neurons, interneurons and dorsal sensory neurons. The absence of Gli2b gene causes defects in the neural tube, involving the decrease of mitotic neural precursors [39-41]. The results from Kanungo J et al revealed that ketamine induced repression of Gli2b gene. In that way it can also be responsible for the reduction of motor or sensory neuron in zebrafish.

Functional damage of ketamine in zebrafish's nervous system

Present studies, which are about nervous system functional damage of zebrafish after ketamine exposure, mainly conduct behavior tests. Prior to or parallel with physical damage, eccentric behavior resulted from ketamine exposure should be essential to evaluate its neurotoxicity. Most researches employed highly trained observers with video cameras and computer software to record and analyze aberrant behavior phenotypes of zebrafish. These behavior experiments include locomotion assay, shoaling test, stress reaction and advanced cognitive function test [42-45]. And the range of dosages used in most behavior studies is also under the sub-threshold (sub-anesthetic) dose [28].

A group of scientists reported that agitation and inhibition effect of larval zebrafish are associated with ketamine dosages. Subanesthetic dosage induced excited behavior phenotypes, but anesthetic dosage induced depressive ones. Besides, they also implied that the agitation might be positively correlated to dopamine release in central nervous system. [19]. Thereby we can assume that it should be a complicated process after ketamine exposure, which is consisted of multiple nervous circuits behind different behavior phenotypes. It is supposed that subanesthetic dosages of ketamine blocked NMDA receptors, which might indirectly increase dopamine release, made zebrafish more excited [46]. In the contrary, anesthetic dosages made zebrafish present anesthetic status with fewer movements.

Many studies showed that ketamine exposure produced a consistent circling behavioral in both zebrafish. More interestingly if withdrawing ketamine this abnormal swimming pattern continues for a period of time [19,42]. Meanwhile this same aberrant swimming pattern in zebrafish can be induced by another NMDA receptor blockade, MK801 [47]. These results are pretty similar with the locomotion of rodents induced by NMDA antagonists [48].

To sum up, the alternative activation of NMDA receptors by ketamine exposure might be the cause of odd behavior phenotypes in zebrafish at a large extent. In other words pathways involved in the blockade of NMDA receptor plays an important role of causing nervous system functional damage.

Conclusions obtained by other behavior researches come next. The novel tank test [44] indicated that ketamine exposure can reduce anxiety of larval zebrafish in strange environment, which resembles similar results in mice [61,62]. The shoaling test [45] was designed to examine how ketamine exposure altered social behavior of zebrafish shoals. It turned out that the average inter-fish distances are larger in experimental groups than the control, which means lower degree of anxiety or impaired social interaction ability after ketamine exposure.

With regard to advanced cognitive dysfunction after ketamine exposure, zebrafish larvae performed impaired ability of learning and memory, with a reduced c-fox gene expression. However, ketamine exposure elevated c-fox expression in adult zebrafish [49], which is coherent with behavior-activating properties of this drug, and similar to ketamine-induced c-fos elevation in rodents [50,51]. It is indicated that ketamine may stimulate intelligent activity and increase c-fox expression. But ketamine exposure at early phase, like embryonic period, seems to do harm to the normal intelligence development.

Perspectives

Several limitations exist among present studies about physical damages caused by ketamine. Firstly, longer exposure time of ketamine is needed to induce physical damages but not the functional impairments. And we don't know whether the exact ketamine concentrations in zebrafish are comparable to these in humans' blood level. We might unify the concentration and exposure time in further studies so that results from different lab are all convincible [29,31,42].

Secondly, studies on rodent models have shown up-regulated NMDA receptors may be responsible for mitochondrial dysfunction, oxidative stress and increased intracelluar calcium which eventually lead to ketamine-induced physical damages. These all should be further validated on zebrafish[12,52-54]. And we have no idea whether damaged neurons would recover over time as well. But this questions need to be answered so that we might be able to know whether children will have bad residual effect of ketamine anesthesia.

Thirdly, it is reported that ketamine decrease serum estradiol-17 b levels, which plays critical roles in neurodevelopment and neuroprotection. But how and it is linked to ketamine-induced physical damage need to be verified on zebrafish [55].

Fourthly, according to previous studies, ketamine has a complex pharmacological profile including glutamatergic, monoaminergic, and GABA-ergic activity [54-58]. Thus physical damages caused by ketamine may not be limited to a single mechanism, such as NMDA antagonism. Fortunately there are still so many genetic tools and mutant strains of zebrafish that we can rely on to further identify how unknown mechanisms and the timing of exposure involved in physical damages induced by ketamine.

During behavior tests, a wider range of behavioral domains may need further studies, such as sensory functions, cognition and aggression, as well as age, sex and strain differences in zebrafish [49]. More importantly, researchers haven't identified whether physical damage is related to or after functional damage yet. We may also take advantages of neurological functional imaging techniques and specific neuron markers to locate dysfunctional areas linked to phenotype accordingly nervous system, which will help us to understand what it is behind the abnormal behavior phenotypes much better.

Since it is reported that co-treatment with acetyl L-carnitine would be neuroprotective [31,59,60]. And it has been shown that acetyl L-carnitine's can provide protection against ketamine-induced decrease in heart rate and ERK/MAPK activity though calcium-modulated signaling [61,62]. Further studies are needed to elucidate the mechanism about how acetyl L-carnitine counteracts ketamine's adverse effects on neurons. And with the help of hb9: GFP strains we can test more other neuroprotective molecules to see if they also can reverse ketamine toxicity effectively.

Conclusions

Current results have demonstrated that for a certain degree ketamine exposure is harmful to the nervous system development. The emphasis in this Review has been to highlight that the zebrafish is a new adequate platform for studying neurodevelopmental toxicity induced by ketamine. Most prior studies focused on neurodevelopmental toxicity of ketamine conducted on traditional animal models such as mice. On the contrary every experiment we reviewed has had carried on the exploration from the different zebrafish phenotypes to the molecular mechanisms and they all showed that zebrafish appeared to be a well substituted animal model for neurochemical dysfunction.

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