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REVIEW ARTICLE

Glutamate NMDA Receptor Antagonists with Relevance to Schizophrenia: A Review of Zebrafish Behavioral Studies

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Abstract: Schizophrenia pathophysiology is associated with hypofunction of glutamate NMDA receptors (NMDAR) in GABAergic interneurons and dopaminergic hyperactivation in subcortical brain areas. The administration of NMDAR antagonists is used as an animal model that replicates behavioral phenotypes relevant to the positive, negative, and cognitive symptoms of schizophrenia. Such models overwhelmingly rely on rodents, which may lead to species-specific biases and poor translatability. Zebrafish, however, is increasingly used as a model organism to study evolutionarily conserved aspects of behavior. We thus aimed to review and integrate the major findings reported in the zebrafish literature regarding the behavioral effects of NMDAR antagonists with relevance to schizophrenia. We identified 44 research articles that met our inclusion criteria from 590 studies retrieved from MEDLINE (PubMed) and Web of Science databases. Dizocilpine (MK-801) and ketamine were employed in 29 and 10 studies, respectively. The use of other NMDAR antagonists, such as phencyclidine (PCP), APV, memantine, and tiletamine, was described in 6 studies. Frequently reported findings are the social interaction and memory deficits induced by MK-801 and circling behavior induced by ketamine. However, mixed results were described for several locomotor and exploratory parameters in the novel tank and open tank tests. The present review integrates the most relevant results while discussing variation in experimental design and methodological procedures. We conclude that zebrafish is a suitable model organism to study drug-induced behavioral phenotypes relevant to schizophrenia. However, more studies are necessary to further characterize the major differences in behavior as compared to mammals.

Keywords: Schizophrenia, zebrafish, behavior, MK-801, ketamine, PCP, psychosis, glutamate antagonists.

1. INTRODUCTION

Schizophrenia is a chronic and heterogeneous neurodevelopmental mental disorder with a lifetime prevalence of 1% [1]. This condition is characterized by a series of complex positive (delusions, hallucinations, disorganized speech), negative (reduction in spontaneous speech, affective flattening, anhedonia, and social withdrawal), and cognitive symptoms (deficits in memory, attention, and executive function) [1]. These symptoms are disabling and it is estimated that the life expectancy of patients with schizophrenia is reduced by 20 years compared with the general population [2]. Antipsychotic drugs are relatively effective in treating positive symptoms; however, they are not effective against the negative and cognitive symptoms, strongly associated with functional impairment [1]. The mechanisms underlying schizophrenia pathophysiology are not completely understood, but the involvement of glutamatergic, GABAergic, and dopaminergic dysfunction has been noted in clinical and preclinical studies [3, 4]. The hypofunction of NMDA receptors (NMDAR) in fast-spiking parvalbumin-positive GABAergic interneurons may trigger an imbalance in brain circuits resulting in dopaminergic hyperactivity in subcortical areas [5, 6].

Animal models of schizophrenia enable the investigation of schizophrenia neurobiology and the search for new therapeutic interventions [7]. Administration of NMDAR antago-

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nists, such as ketamine [8] or PCP [9], induces delusions and hallucinations in healthy individuals and exacerbates negative and cognitive symptoms in patients with schizophrenia [10, 11]. NMDAR antagonists have thus been used to mimic NMDAR hypofunction and serve as an important pharmacological tool in animal models of schizophrenia. Hyperlocomotion and stereotypic behavior are robust behavioral changes observed after exposure to NMDAR antagonists, such as MK-801, ketamine, and PCP. They are often related to positive symptoms as they result from hyperactivity in dopaminergic neurons [11]. Moreover, NMDAR antagonists induce behavioral changes related to negative and cognitive symptoms, such as memory impairment, sensorimotor deficit, and social interaction dysfunction [12]. These drugs thus lead to behavioral changes that resemble the full spectrum of positive, negative, and cognitive symptoms observed in patients with schizophrenia [5, 6, 13, 14].

Together with statistical and methodological inconsistencies, species-specific characteristics of the animal models are another extremely relevant source of bias in behavioral neuroscience [15, 16]. Researchers have focused on a few species to conduct their experiments throughout the years, even though a vast range of behavioral responses are singularly displayed by some species. Mice and rats are the most frequently used model organisms in behavioral science. However, this overwhelming reliance on rodents may lead to species-specific biases and poor translatability, which could be avoided by cross-species approaches and a focus on evolutionarily conserved aspects of behavior [15, 17]. It may also lead to overinterpreted or simplified findings when data from other animals are not available, impacting the translation of animal results to human conditions [18].

In the last years, a series of publications have endorsed the use of zebrafish as an alternative model animal to study brain disorders and conduct high-throughput drug screening for potential novel treatments [19-21]. Although several studies investigated the effects of NMDAR antagonism in zebrafish, some findings are inconclusive, conflicting, or lack replication. We thus aimed to review and integrate the major findings reported in the zebrafish literature regarding the behavioral effects of NMDAR antagonists with relevance to schizophrenia.

We conducted a literature search for "zebrafish AND ('glutamatergic antagonist' OR 'NMDA antagonist' OR dizocilpine OR MK-801 OR ketamine OR phencyclidine OR PCP OR memantine)" limited to January 1st 2000 and September 30th 2020 in MEDLINE *via* PubMed (n=293) and Web of Science (n=345) databases. After the removal of duplicates, the total number of records was n=393. We then excluded 266 entries based on title and abstract screening for the following reasons: review articles, retracted articles, conference abstracts, book chapters, not available in English, no use of zebrafish as a model organism, no report of behavioral outcomes, and no administration of an NMDA antagonist drug. The full-texts were analyzed from the remaining 127 studies, and we excluded 83 based on the same criteria. A final 44 articles were included in this review. A detailed overview of the studies is presented in Table **1**.

2. ZEBRAFISH AS A MODEL ORGANISM FOR MODELING SCHIZOPHRENIA

The use of zebrafish as a model organism is quite recent as compared to other animals. It has been increasingly recognized that zebrafish is suitable as an alternative model to broaden the number of species used in behavioral science, allowing the comparison of interventions on species with distinct natural histories [22-24]. Although zebrafish are simple organisms making them an easy target for genetic manipulation [25], they present highly genetic homology to humans [25, 26]. Thus, a series of complex behaviors can be readily analyzed in this experimental model [27, 28]. Zebrafish also offer numerous other advantages, such as their low cost for acquisition and maintenance, easy reproduction, and rapid development compared to other animals [27]. Taken together, these characteristics reinforce the potential of zebrafish as a tool to study mechanisms and treatments for brain disorders such as anxiety, epilepsy, and schizophrenia [19-21, 23, 29].

Zebrafish possess a conserved neuronal architecture, with cells, neurotransmitters, and receptors analogous to those present in mammals [30]. These similarities point to the possibility of inducing schizophrenia-like phenotypes in zebrafish and investigating the impact of psychotropic drugs on the behavior and neurochemistry of zebrafish. Catecholaminergic neurons and dopaminergic receptors with structure and function similar to those of mammals can be found in different zebrafish brain regions like the diencephalon and telencephalon [30-33]. Glutamatergic and GABAergic pathways, important for regulating the activity of dopaminergic neurons, are present as well, integrating both interneuron systems and long pathways [34]. Zebrafish present conserved families of NMDAR [35], the target of drugs such as dizocilpine (MK-801), and ketamine. On the other hand, GABA is extensively produced in the brain and spinal cord of zebrafish by interneurons, helping modulate different neural systems related to schizophrenia and several other conditions [36].

There are some important differences between the glutamatergic system of zebrafish brain compared to mammals, mainly in the number of genes encoding proteins, as a result of the teleost gene duplication event [37]. In most cases, zebrafish have multiple paralogs for each human gene and have 13 putative genes that code for NMDA-type ionotropic receptors, while humans have 7 [37]. Some genetic manipulation studies highlight the importance of the GluN1 receptor subunits. CRISPR-mediated manipulations to the genes grin1a and grin1b, which encode obligatory GluN1 receptor subunits, have been reported in zebrafish [38]. The knockout of both these genes directly impairs NMDAR-mediated synaptic transmission and the mutant animals present some atypical behaviors such as hyperactivity, deficits in prey capture, and abnormal responses to light and acoustic stimuli [38]. The glutamatergic system, including its main components, metabolic pathways and function, is shared and analogous between zebrafish and mammals [37]. To our knowledge, there are no studies in the literature that investigated the pharmacodynamic mechanisms of the binding of NMDAR antagonists in the zebrafish brain. However,

Table 1. Published studies reporting zebrafish behavioral analysis involving NMDA antagonists.

Drug	Delivery/Duration	Concent/Dose	Age	Behavioral Domain	Main Findings	Refs.
APV	Water, acute	100, 200 µM	6-8 dpf	Sensory response	**Rapid escape reflex** ↑ startle response	[121]
Ketamine	Water, acute	0.2% (v/v)	4-8 mpf	Locomotion; stress response	**Locomotor activity** ↑ circling behavior **Ventilatory response to hypoxia** ↓ gill movements **Response to hypoxic stress** ↓ response (body pulses)	[93]
		2, 20, 40 mg/L	5-7 mpf	Locomotion; anxiety; social behavior	**NTT** ↑ rotations ↑ time in the upper zone ↓ latency and transitions to the upper zone = distance traveled **OTT** = circling behavior = distance traveled and speed **LDT** ↑ entries and time in the white zone **SI** ↑ inter-fish distance ↑ entries in all arms	[94]
		5, 20, 40, 60 mg/L	6-8 mpf	Anxiety	**LDT** ↓ latency to enter the white zone ↑ time in the white zone and crossings = average entry duration	[96]
		2, 20, 40 mg/L	4-6 mpf	Aggressiveness; locomotion	**Aggressiveness** ↑ aggressive episodes (latency to attack and time spent in the mirror zone) ↓ absolute turn angle ↑ distance traveled and rotations	[97]
		1 g/mL	Adult	Locomotion	**Locomotor activity** ↑ erratic, acceleration, and circular movements	[98]
		0.1, 1, 10, 50 µM	5 dpf	Locomotion	**Locomotor activity** ↑ total distance	[99]
		72.9 µM	28 dpf	Social behavior; aggressiveness	**SI** ↑ inter-fish and nearest neighbor distance **Aggressiveness** ↓ aggressive episodes (time and distance in the mirror zone)	[102]
		0.2, 0.4, 0.8 mg/mL	2, 5, 10 hpf	Locomotion; anxiety; social behavior	**Locomotor activity** ↑ distance traveled in the center zone ↑ time in the upper zone = distance traveled and speed **SI** = inter-fish and nearest neighbor distance	[128]

(Table 1) contd….

Drug	Delivery/Duration	Concent/Dose	Age	Behavioral Domain	Main Findings	Refs.
Ketamine	-	50, 70, 90 mg/L	2 hpf	Locomotion; anxiety; social behavior	**Locomotor activity** ↑ distance traveled in the center zone ↑ avoidance behavior **SI** = inter-fish and nearest neighbor distance	[101]
	Water, chronic	0.2% (v/v)	4-8 mpf	Locomotion, stress response	**Locomotor activity** ↑ circling behavior Ventilatory response to hypoxia ↓ gill movements Response to hypoxic stress ↓ response (body pulses)	[93]
		20 mg/L	> 90 dpf	Anxiety	**NTT** = time in the upper zone	[95]
Memantine	Water, acute	5, 10, 20, 50, 100 µM	5 dpf	Locomotion	**Locomotor activity** = speed	[78]
		3, 10, 30 µM	6 dpf	Sensory response	**Acoustic startle response** ↑ distance traveled in response to auditory stimuli	[119]
MK-801	i.c.v. injection	8-12 nL of 100 µM/fish	24 hpf	Sensory response	**Spontaneous coiling** = duration of spontaneous coiling ↑ touch response	[83]
	i.m. injection	10 µg/fish	Adult	Learning and memory	**Active avoidance** = memory retention (association between light and shock)	[64]
	i.p. injection	0.1, 0.3, 0.5, 1, 2 mg/kg	4 mpf	Learning and memory	**Inhibitory avoidance** ↓ latency to enter the dark zone (memory impairment) **NTT** ↑ distance and time in the upper = male and female Taurine prevented these effects	[61]
		0.2, 2 mg/kg	4 mpf	Anxiety	**LDT** ↑ time, entries, and distance in the white zone ↑ thigmotaxis	[81]
	r.o. injection	4 µL of 12.5 µM/fish	6-12 mpf	Locomotion; anxiety; social behavior	**NTT** = distance, speed, meander, freezing, latency to the upper zone **SI** = inter-fish distance	[72]
	Water, acute	0.1, 1 µM	10 dpf	Learning and memory	**NOR** = postures and eye movement towards the novel objects	[58]
		20 µM	Adult	Learning and memory	**Inhibitory avoidance** ↓ latency to enter the dark zone (memory impairment)	[59]
		5 µM	< 8 mpf	Learning and memory; social behavior	**Inhibitory avoidance** ↓ latency to enter the dark zone (memory impairment) **SI** ↓ time in the interaction zone Sulpiride and olanzapine, but not haloperidol, reversed these effects	[60]

(Table 1) contd….

Drug	Delivery/ Duration	Concent/ Dose	Age	Behavioral Domain	Main Findings	Refs.
MK-801	-	20 μM	3-6 mpf	Learning and memory; locomotion	**Inhibitory avoidance** ↓ latency to enter the deep zone (memory impairment) **Locomotor activity** = distance and mean speed	[63]
		20 μM	3-12 mpf	Learning and memory	**Contextual fear conditioning** ↓ distance associated with shock (memory impairment)	[62]
		2, 20, 100 μM	6-8 mpf	Locomotion; anxiety; social behavior	**OTT** ↑ circling behavior = creeping, thrashing on the side, thrashing on the bottom, floating, foraging, freezing, sinking, swimming, tilting, jumping **LDT** = time in the white zone **SI** ↓ time in the interaction zone	[68]
		5, 10, 20 μM	> 8 mpf	Learning and memory; locomotion	**Y-maze** ↓ time in the novel arm (memory impairment) **Locomotor activity** = distance, speed, absolute turn angle, crossings	[65]
		5, 10 μM	6-7 mpf	Learning and memory	**NOR** ↓ time exploring new object (memory impairment) ↑ distance traveled ↓ immobile time	[67]
		100 μM	21 dpf	Social behavior	**SI** ↓ time in the social zone = locomotor activity	[69]
		5 μM	6-8 mpf	Social behavior; aggressiveness	**SI** ↓ time in the social zone **Aggressiveness** ↓ time in the opponent zone Oxytocin and carbetocin prevented these effects	[70]
		1, 2, 5 μM	6 mpf	Social behavior	**SI** ↓ inter-fish distance ↑ distance	[71]
		100, 200, 400 nM	3 dpf	Locomotion	**NTT** = distance and speed	[129]
		5, 10, 15, 20 μM	12 mpf	Locomotion	**NTT** ↑ distance	[73]
		20 μM	Adult	Locomotion; anxiety	**NTT** ↑ total distance, speed, and time in the upper zone Haloperidol and olanzapine reversed these effects	[74]
		2, 20 μM	Adult	Locomotion; preference	**OTT** ↑ circling behavior ↓ crossings ↑ time in the upper zone **Place preference** ↓ time in the enriched chamber = male and female	[75]

(Table 1) contd….

Drug	Delivery/ Duration	Concent/ Dose	Age	Behavioral Domain	Main Findings	Refs.
-	-	20 μM	6 dpf	Locomotion; predatory behavior	**Locomotor activity** ↓ spontaneous activity ↑ swim length and speed **Predatory behavior** ↓ paramecium captured	[38]
		1, 5, 20 μM	30, 60, 120 dpf; 2 ypf	Locomotion; anxiety	**NTT** ↑ distance and time in the upper zone	[76]
		5, 20, 100, 200 μM	7 dpf	Locomotion	**Locomotor activity** ↑ AB strain distance traveled ↓ TU strain distance traveled	[77]
		1, 5, 10, 20, 50, 100 μM	5 dpf	Locomotion	**Locomotor activity** ↑ spontaneous locomotion SKF-83566 and sulpiride did not alter these effects	[78]
		1, 5, 20 μM	15 dpf	Locomotion	**NTT** ↓ distance	[79]
		5, 10, 15, 20 μM	6-8 mpf	Anxiety	**OTT** ↑ time in the upper zone Caffeine and DPCPX prevented this effect	[80]
		10, 20, 50, 100, 200 μM	7 dpf	Anxiety	**LDT** ↓ distance traveled under light and dark	[82]
		20 μM	Adult	Learning and memory	**Passive avoidance** ↓ latency to enter the dark zone (memory impairment)	[130]
		20 μM	6-8 mpf	Learning and memory	**Plus maze** ↓ latency to enter and time in the conspecifics chamber (memory impairment)	[66]
PCP	Water, acute	0.5, 1; 3 mg/L	5-8 mpf	Locomotion; anxiety; social behavior	**NTT** ↓ latency to the upper zone, freezing, and immobility ↑ erratic movements = distance traveled and speed **OTT** ↑ circling **SI** = inter-fish and nearest neighbor distance	[111]
		3 mg/L	5-7 mpf	Locomotion; anxiety	**NTT** ↑ circling behavior	[112]
Tiletamine	Water, acute	1, 5, 10 mg/L	5-7 mpf	Locomotion; anxiety	**NTT** ↓ entries to the upper zone ↑ erratic movements and freezing	[120]

Abbreviations: APV, DL-2-amino-5-phosphonopentanoic acid; concent, concentration; dpf, days post-fertilization; DPCPX, selective adenosine A1 receptor antagonist; hpf, hours post-fertilization; i.c.v., intracerebroventricular; i.p., intraperitoneal; LDT, light/dark test; MK-801, dizocilpine; mpf, months post-fertilization; NOR, novel object recognition; NTT, novel tank test; OTT, open tank test; PCP, phencyclidine; r.o., retro-orbital; SI, social interaction test; SKF-83566, selective D1 receptor antagonist; water, water exposure; ↑, increased or higher as compared to control group; ↓, decreased or lower as compared to control group; =, no difference compared to control group.

the glutamatergic similarities point to a similar mechanism of action of NMDAR antagonists between zebrafish and mammals.

This intricate network of neurons, neurotransmitters, and receptors preserved throughout the vertebrates allows researchers to create and adapt models relevant to schizophrenia using different animals, like the zebrafish, to push forward the knowledge on this field. However, a full picture of the zebrafish behavioral repertoire that is reliably altered by interventions known to induce schizophrenia-like pheno-

types in mammals is needed to identify eventual differences and limitations of this species.

3. GLUTAMATE NMDA RECEPTOR ANTAGONISTS AS PHARMACOLOGICAL TOOLS TO MODEL SCHIZOPHRENIA

The ionotropic NMDAR is a cation channel that produces excitatory postsynaptic potentials when activated and has an important role in a series of brain functions, such as learning, memory, and synaptic plasticity [39]. Several studies have shown that NMDAR antagonists can induce transient schizophrenia-like symptoms in animals and humans [40-42]. Besides that, exposure to these drugs can exacerbate symptoms in patients [43]. Studies using imaging techniques and postmortem analysis of the brain of patients with schizophrenia, as well as results obtained from experiments with animal models, [13, 44, 45] have suggested there is a dysregulation of hippocampal and cortical fast-spiking GABAergic parvalbumin-positive interneurons and hypofunctional NMDAR expressed by these interneurons, which leads to altered excitation-inhibition balance in cortical and subcortical areas of the brain [46-48]. Studies in animal models of schizophrenia have an indispensable role in our understanding of the etiopathogenesis of this condition. Furthermore, animal models in scientific research are an important tool for developing new treatments with therapeutic potential.

Early administration of NMDAR antagonists to rodents [49] and marmoset [50, 51] can mimic aspects of the schizophrenia pathology, assuming that a disturbance during pre- or perinatal brain development results in the manifestation of schizophrenia-like phenotypes in early adulthood [49]. The behavioral changes observed are related to the positive, negative, and cognitive symptoms of schizophrenia, such as hyperlocomotion and stereotypy (related to dopaminergic hyperactivation), deficits in information processing, impairment of cognitive functions (working memory and attention), and social interaction deficits [52]. This pharmacological induction of NMDAR hypofunction leads to disinhibition of excitatory hippocampal neurons and, consequently, disruption of the firing of dopaminergic neurons in the mesolimbic and mesocortical pathways [5, 53]. Acute administration of NMDAR antagonists induces schizophrenia-like symptoms in animals, and this model is often used to predict the effects of drugs with potential antipsychotic properties [54]. Animal models based on repeated administration of NMDAR antagonists can change neurotransmitter systems in the long-term and better recapitulate the natural course and neurobiological alterations associated with schizophrenia.

3.1. Dizocilpine (MK-801)

MK-801 is a potent non-competitive NMDAR antagonist frequently used as a pharmacological tool in rodent schizophrenia models [5, 53]. It is also the more frequently used NMDAR antagonist in zebrafish behavioral studies, accounting for 64.5% of the publications reviewed here (Fig. **1**). In the rodent literature, experimental protocols employ repeated administration of MK-801 in neonatal [55, 56] or adult animals [11]. Acute administration is also used to assess sensitivity to drug-induced locomotor activity [57] in other rodent models of schizophrenia (*e.g.*, neonatal lesion of the ventral hippocampus). Studies evaluating the effects of MK-801 on zebrafish behavior mainly assess behavioral paradigms such as learning and memory, social behavior, locomotion, and anxiety (Fig. **1**). Although most experimental protocols vary widely between studies and conflicting findings were reported, some effects such as social and memory deficits seem robust and replicated by different research groups (Fig. **3**).

Most studies have found that MK-801 impairs learning and memory in adult zebrafish, but not in larvae [58]; the inhibitory avoidance protocol was frequently used to assess learning and memory in these studies [59-63]. On the other hand, Xu *et al*. (2007) [64] did not find any effects induced by MK-801 in an active avoidance paradigm. MK-801 also impaired learning and memory in maze tasks [65, 66] and the novel object recognition test [67]. Interestingly, Cognato *et al*. (2012) [65] reports that the experiments were performed using only male zebrafish.

The effects of MK-801 on social behavior in adult zebrafish are robust as most of the reviewed studies observed social interaction deficits without locomotor changes. Seibt *et al*. (2011) [60], Sison *et al*. (2011) [68], Dreosti *et al*. (2015) [69] and Zimmermann *et al*. (2016) [70] observed that MK-801-treated animals present reduced social interaction as compared to controls in a test that measured the time fish spent near a tank containing conspecifics. Interestingly, Seibt *et al*. (2011) [60] performed the experiments using only males and observed that the atypical antipsychotics sulpiride and olanzapine, but not the typical antipsychotic haloperidol, reverse the social deficit. Zimmermann *et al*. (2016) [70] found that oxytocin and carbetocin prevent the social deficit induced by MK-801. In a study performed by Maaswinkel *et al*. (2013) [71], MK-801-induced social deficit was shown by reduced social cohesion in a test that evaluates inter-individual distance in a group of female fish. Only McCutcheon *et al*. (2017) [72] did not find any differences between control and MK-801-treated fish in a shoaling test. However, the administration route was a retro-orbital injection, unlike other studies that performed drug administration *via* aqueous exposure.

Regarding the effects of MK-801 on locomotor activity in adult zebrafish, Tran *et al*. (2016) [73] and Seibt *et al*. (2010) [74] found an increase in total distance traveled, mean speed, and time spent in the upper zone following MK-801 exposure in the novel tank test (NTT). Interestingly, Tran *et al*. [73] observed that hyperlocomotion induced by MK-801 was context-dependent, as it only occurs when the animal is subjected to a new environment (NTT), and no differences were observed when exposure to MK-801 occurs in the house tank. On the other hand, McCutcheon *et al*. (2017) [72], Sison *et al*. (2011) [68], Cognato *et al*. (2012) [65] and Ng *et al*. (2012) [63] failed to observe locomotor changes after MK-801 exposure. Swain *et al*. (2004) [75] observed that adult zebrafish exposed to MK-801 presented more circling behavior than control animals, along with increased time spent in the upper zone of the NTT. The results for MK-801 locomotor effects in larvae are equally conflicting as some articles report higher [38, 76-78], lower [79], or equal levels of locomotor activity as compared to control animals [72].

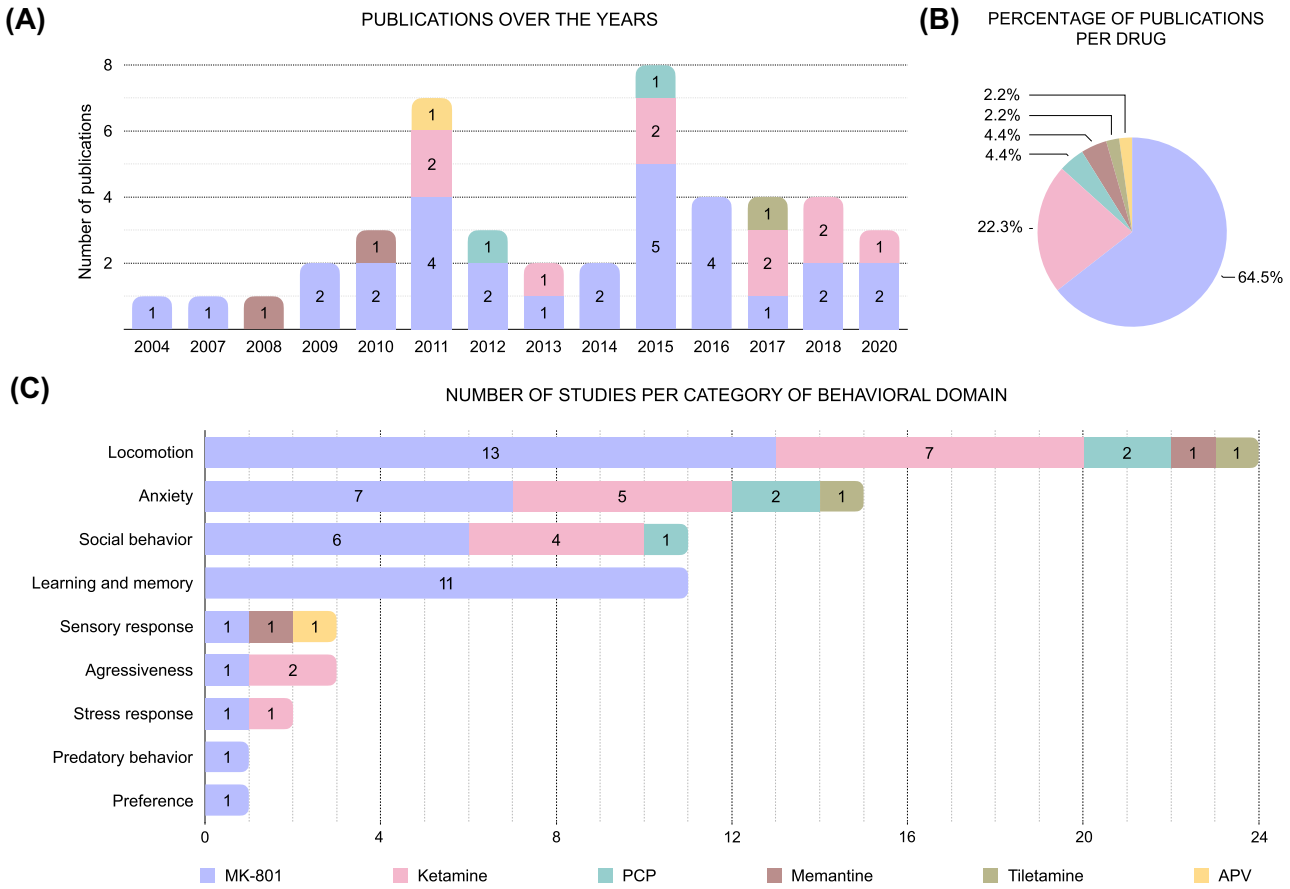

Fig (1). A quantitative overview of the studies reporting the use of NMDAR antagonist drugs (MK-801, ketamine, PCP, memantine, tiletamine, and APV) in zebrafish behavioral research published in peer-reviewed scientific journals between 2000 and 2020. (**A**) The number of publications per year with each drug. (**B**) Percentage of publications with each drug. (**C**) The number of publications per behavioral domain with each drug. APV, DL-2-amino-5-phosphonopentanoic acid, MK-801, dizocilpine; PCP, phencyclidine. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The effects on other behavioral domains, such as anxiety, sensory response, aggressiveness, and predatory behavior, are less well characterized. However, in the NTT, fish exposed to MK-801 spent more time in the upper zone of the tank [74, 76, 80], which is typically considered an anxiolytic effect. However, as MK-801 altered locomotor activity, including stereotypy-related behaviors such as circling [68], the increased time spent in the upper zone may be better explained by modulation of locomotor instead of anxiety pathways. While Herculano *et al*. (2015) [81] found that MK-801 increases time spent in the white zone during the light/dark test, Sison *et al*. (2011) [68] and Li *et al*. (2018) [82] found no significant differences between treated animals and controls. Pietri *et al*. (2009) [83] found that larvae exposed to MK-801 had an increase of touch response, a sensory response. In the predatory behavior, MK-801 treated larvae captured fewer paramecia as compared to controls [38]. Furthermore, MK-801-treated zebrafish adults were less aggressive than controls in the mirror stimulus-response test [70].

3.2. Ketamine

Ketamine, a dissociative anesthetic, also acts as a non-competitive antagonist of NMDAR [84]. It is also a drug of abuse known as special K, popular in raves and clubs. This drug provokes pro-psychotic effects in healthy individuals [13] and exacerbates psychosis in schizophrenia patients [43, 85]. When administered to rodents, ketamine can generate a series of behavioral and neurochemical alterations that resemble the deficits shown by schizophrenia patients [86].

In rodents, acute administration of ketamine elicits cognitive impairment, disruption of prepulse inhibition of the startle reflex, hyperlocomotion, and social interaction deficits [87-89]. Repeated administration induces the same behavioral phenotypes [90] but also leads to loss of parvalbumin-expressing interneurons [91] and hippocampal hyperactivity [92].

Classical protocols used to evaluate zebrafish behavior, such as the NTT, have been used to understand the impacts of ketamine on fish behavior. When exposed to this drug, zebrafish show behavioral alterations similar to those seen in other animal models. Zakhary *et al*. (2011) [93] demonstrated that acute or repeated exposure (daily for five days) of adult zebrafish leads to increased circling behavior along with decreased gill movements and body pulses in response to stress. Riehl *et al*. (2011) [94] reported that ketamine-treated animals presented more circling behavior, fewer transitions to the upper area of the tank, and more time in this

zone than controls. Pittman and Hylton (2015) [95], on the other hand, reported that repeated ketamine exposure (daily for two weeks) had no impact on the time spent in the upper area of the tank. In the light/dark test, ketamine was associated with more transitions [94, 96] and more time spent in the white area [96]. In a shoaling, test ketamine was observed to increase the average inter-fish distance [94]. Aggressive behavior was also modulated by ketamine: Michelotti *et al*. (2018) [97] reported that lower doses of ketamine enhanced aggressive behavior while higher doses had the opposite effect, reducing the number and duration of aggressive episodes. Furthermore, when using this drug to anesthetize the fish, Martins *et al*. (2018) [98] described that, before the loss of reflexes, zebrafish presented phases of intense, erratic, and circular movements.

Experiments on early developmental stages can also recapitulate behavioral phenotypes observed on schizophrenia models. Suen *et al*. (2013) [99] showed that lower ketamine concentrations increase the distance traveled by larvae, while high concentrations had anesthetic effects. Félix *et al*. (2016 and 2017) [100, 101] reported alterations in exploratory behavior, with an increase of distance traveled in the center of the well and enhanced avoidance behavior towards an aversive stimulus. As seen in adults, Shen *et al*. (2020) [102] showed higher nearest neighbor distance and inter-individual distance in larvae exposed to ketamine than controls.

3.3. Phencyclidine (PCP)

Another non-competitive NMDAR antagonist widely used in schizophrenia research is phencyclidine [84]. Similar to ketamine, PCP is also a drug of abuse and is known to induce a psychotic-like state in humans [103]. Different animal models of schizophrenia using PCP have been developed, with either perinatal or adult acute or chronic drug administration [104]. In rodents, PCP treatment in early developmental stages can induce long-lasting schizophrenia-like phenotypes that manifest in the adult stage [105, 106]. In adults, both acute and chronic administration induce hyperlocomotion [107, 108] and cognitive impairment [109, 110]. Chronic adult treatment also elicits long-lasting behavioral abnormalities, as seen in perinatal models [104].

Only a couple of studies exposing adult zebrafish to PCP have been performed. Kyzar *et al*. (2012) [111] reported that exposure to PCP induced anxiety and locomotor changes in the NTT, including increased erratic movements, reduced latency to the upper zone of the tank, freezing bouts, and immobility time. In contrast, in the open tank test (OTT), PCP increased circling behavior. Stewart *et al*. (2015) [112] evaluated the locomotor activity of zebrafish in a three-dimensional setup and also observed more circling behavior in fish exposed to PCP as compared to controls. Although studies using PCP are still scarce, exposure to the drug evoked behavioral alterations compatible with the expected from other animal models of schizophrenia.

3.4. Other Glutamatergic Antagonists

Other NMDAR antagonists were also employed in zebrafish studies. They are less commonly used to recapitulate schizophrenia-like behaviors in animals, but as the pharmacological target is the same, they can nevertheless induce the relevant phenotypes and were thus included in this review. Memantine appeared in 2 publications, while tiletamine and DL-2-amino-5-phosphonopentanoic acid (APV) appeared in only one (Fig. **1**). As reviewed elsewhere [113], memantine, especially in lower doses, can induce similar effects as ketamine on locomotor and cognitive parameters in rodents. Tiletamine also generates effects comparable to ketamine, reducing social interaction time, and inducing learning deficits in the passive avoidance task [114]. In contrast, most of the research carried out using APV focuses on inhibiting long-term potentiation as a tool to understand key factors of learning and memory rather than to study schizo-

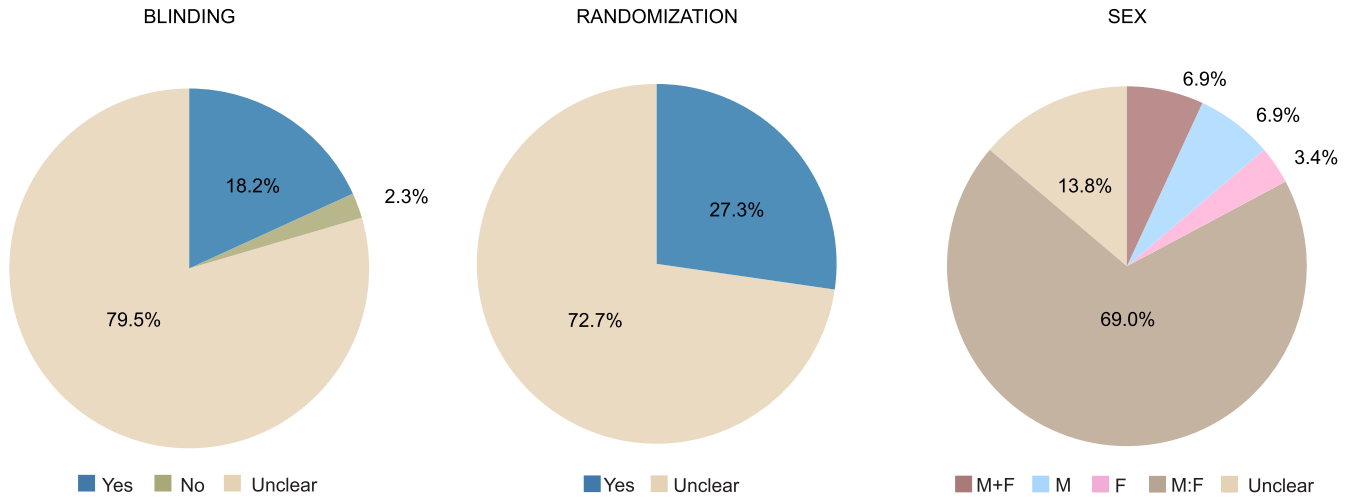

Fig (2). Description of relevant methodological details in the publications included in this review. For blinding and randomization, graphs depict the percentage of publications that reported implementation or not of these practices (unclear was computed when there was no mention). Sex of the animals used was computed as M:F when male and female were included but tested and analyzed as a mixed group, and M+F when male and female fish were discriminated in the experiments. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

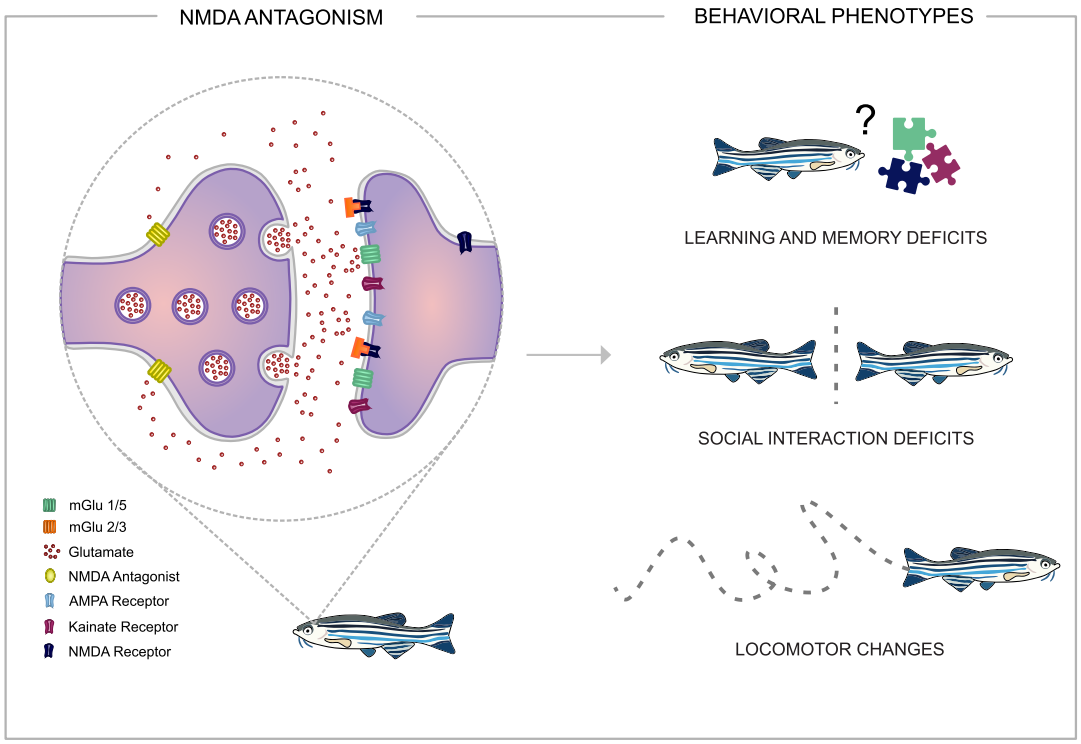

Fig (3). Schematic illustration of the mechanism of action of NMDAR receptor antagonists in the zebrafish brain and behavioral phenotypes induced by the administration of these drugs. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; mGLU, metabotropic glutamate; NMDA, N-methyl-D-aspartate. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

phrenia [115, 116]. Unlike the other NMDAR antagonist reviewed here, memantine is shown to inhibit distinct subpopulations of receptors depending on the intensity and duration of its activation [117, 118]. Such selectivity may explain the divergent clinical effects compared to the other drugs and could implicate in contrasting outcomes in the behavior of animals.

Best *et al*. (2008) [119] reported that zebrafish larvae exposed to memantine display augmented startle response to an acoustic stimulus. Chen *et al*. (2010) [78] reported that memantine has no effects on the locomotor parameters of zebrafish larvae. In adult zebrafish, tiletamine reduced the upper zone entries and increased erratic movements and freezing frequency and duration in the NTT [120]. Roberts *et al*. (2011) [121] reported that APV reduces the habituation index after spaced training to an acoustic stimulus. Although research investigating these drug effects in zebrafish is still scarce and needs to be replicated, they are important to highlight the importance of NMDAR antagonism as a tool to investigate the mechanisms underlying zebrafish behavior in several domains.

4. REPRODUCIBILITY CHALLENGES

Reproducibility issues are increasingly discussed by the scientific community [122], including zebrafish neuroscience and behavioral researchers [16]. Although variation in protocols and methodologies adopted by different research groups have been pointed out as a source for inconsistent data in preclinical research, standardization is not likely to be a major solution for this problem [123, 124]. Nevertheless, several experimental protocols differed between the studies regarding the size or type of the apparatus used, zebrafish strain and age, drug delivery route, and time and frequency of exposure to drugs, among others (Table **1**). Such differences in methodology among the research groups may explain, at least in part, the conflicting results reported for behavioral parameters such as locomotion, exploratory behavior, and anxiety.

Furthermore, some replication challenges could be avoided by improved reporting of methodological procedures and open access to protocols, code, and data [125, 126]. The critical assessment of the validity of a study's findings also requires that relevant information regarding the experimental design and statistical analysis is reported in detail, including blinding, randomization, and sample size calculation procedures [125]. A matter of concern is that, with rare exceptions, the studies reviewed here did not describe the blinding and randomization procedures used, or if they were even used (Fig. **2**). Most of the studies did not state whether the sample size was calculated a priori or whether a criterion was used for removing outliers. This lack of information and description precludes the assessment of whether good research practices and experimental planning were followed.

As zebrafish have almost no prominent sexually dimorphic characteristics, it is quite hard for researchers to visually identify the sex of the animals *in vivo* and take this biological variable into account when evaluating behavioral parameters. The few studies that discriminate male and female zebrafish frequently fail to report how sexual characteriza-

tion was made. Most of the studies reviewed here used a mixed pool of male and female animals and, therefore, did not evaluate any possible sex influence on the effects of NMDAR antagonism (Fig. **2**). Reviews on the literature demonstrate the importance of studying both sexes in animal models of schizophrenia since there are clinical differences between men and women with schizophrenia. Male and female rodents also display significant differences in response to behavioral testing and treatment [127]. Considering sex as a biological variable is important to understand and delineate better schizophrenia-like endophenotypes in zebrafish and improve the reproducibility of findings across laboratories.

As the use of zebrafish as a model organism for the study of relevant aspects of schizophrenia is relatively recent, there are few studies investigating the predictive validity of zebrafish behavioral assays. Of the 44 articles described in this review, only 3 assessed the effects of antipsychotic drugs on reversing or preventing MK-801-induced changes (there are no data with the other NMDAR antagonists). As mentioned in the table, the antipsychotics haloperidol, sulpiride, and olanzapine [60, 74] were able to prevent locomotor, cognitive, and social alterations MK-801-induced, highlighting the predictive validity of the tests. This reinforces the need to further evaluate the effects of antipsychotic drugs in relevant zebrafish behavioral assays and better assess the predictive validity of pharmacological models of schizophrenia in zebrafish.

CONCLUSION

Deficits in social interaction and memory impairment induced by MK-801 and circular behavior induced by ketamine were the most frequently reported findings in the zebrafish literature reviewed here. However, mixed results have been observed for locomotor and anxiety parameters, which can be at least in part explained by a large variation in experimental design. This review integrated the most relevant findings reported in the zebrafish literature on schizophrenia-relevant behavioral effects of NMDAR antagonists. We conclude that zebrafish is a model organism suitable for studying drug-induced behavioral phenotypes relevant to schizophrenia, however further studies are needed to further characterize the main differences in behavior compared to mammals.

LIST OF ABBREVIATIONS

APV	=	DL-2-amino-5-phosphonopentanoic acid
DPCPX	=	Selective adenosine A_1 receptor antagonist
dpf	=	Days post-fertilization
hpf	=	Hours post-fertilization
i.c.v.	=	Intracerebroventricular
i.p.	=	Intraperitoneal
LDT	=	Light/dark test
MK-801	=	Dizocilpine
mpf	=	Months post-fertilization
NOR	=	Novel object recognition
NTT	=	Novel tank test
OTT	=	Open tank test
PCP	=	Phencyclidine
r.o.	=	Retro-orbital
SI	=	Social interaction tests
SKF-83566	=	Selective D_1 receptor antagonist

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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