



Zebrafish as a potential non-traditional model organism in translational bipolar disorder research: Genetic and behavioral insights

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ABSTRACT

Bipolar disorder (BD) is a severe and debilitating illness that affects 1–2% of the population worldwide. BD is characterized by recurrent and extreme mood swings, including mania/hypomania and depression. Animal experimental models have been used to elucidate the mechanisms underlying BD and different strategies have been proposed to assess BD-like symptoms. The zebrafish (*Danio rerio*) has been considered a suitable vertebrate system for modeling BD-like responses, due to the genetic tractability, molecular/physiological conservation, and well-characterized behavioral responses. In this review, we discuss how zebrafish-based models can be successfully used to understand molecular, biochemical, and behavioral alterations paralleling those found in BD. We also outline some advantages and limitations of this aquatic species to examine BD-like phenotypes in translational neurobehavioral research. Overall, we reinforce the use of zebrafish as a promising tool to investigate the neural basis associated with BD-like behaviors, which may foster the discovery of novel pharmacological therapies.

1. Introduction

Bipolar disorder (BD) is a chronic and debilitating illness, characterized by extreme mood swings, varying from mania/hypomania and depression (Grande et al., 2016). This condition has a prevalence of 1–2% among the population worldwide (Disease et al., 2018). Currently, two major types of BD have been reported, known as bipolar I disorder (BD-I) and bipolar II disorder (BD-II) (Severus and Bauer, 2013). While BD-I has been recognized by alternation between manic and depressive episodes, in BD-II occurs at least one depressive and one hypomanic episode, but not mania (Gould and Einat, 2007; Grande et al., 2016). Manic episodes include hyperactivity, euphoria, increased self-esteem, aggression, irritability, reduced sleep, hypersexuality, and sometimes psychosis (Kopeykina et al., 2016; Mason et al., 2016; McElroy et al., 2016). Conversely, depressive episodes involve other manifestations,

such as persistent sadness, decreased energy, anhedonia, social withdrawal, psychomotor retardation, and low self-esteem (Caligiuri and Ellwanger, 2000; Mason et al., 2016; Nofzinger et al., 1991). Hypomania is a milder form of mania with reduced symptoms severity which usually does not require medical assistance (Anderson et al., 2012; Vieta and Rosa, 2007). Since BD treatments (e.g., anticonvulsants and antipsychotics) were developed for treating other brain disorders (e.g., epilepsy and schizophrenia), the existing pharmacological therapies may have limited efficacy (Dodd et al., 2015). Thus, improving the validation of experimental animal systems to model BD-like phenotypes is an interesting strategy to elucidate the evolutionarily conserved mechanisms underlying BD and search for novel effective therapies.

Although rodents are invaluable systems for investigating the neurobehavioral basis of BD (Paige et al., 2014), it is very difficult to perform high-throughput pharmacological screens and test a wide range

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