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Aquatic blues: Modeling depression and antidepressant action in zebrafish

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ABSTRACT

Depression is a serious psychiatric condition affecting millions of patients worldwide. Unipolar depression is characterized by low mood, anhedonia, social withdrawal and other severely debilitating psychiatric symptoms. Bipolar disorder manifests in alternating depressed mood and 'hyperactive' manic/hypomanic states. Animal experimental models are an invaluable tool for research into the pathogenesis of bipolar/unipolar depression, and for the development of potential treatments. Due to their high throughput value, genetic tractability, low cost and quick reproductive cycle, zebrafish (*Danio rerio*) have emerged as a promising new model species for studying brain disorders. Here, we discuss the developing utility of zebrafish for studying depression disorders, and outline future areas of research in this field. We argue that zebrafish represent a useful model organism for studying depression and its behavioral, genetic and physiological mechanisms, as well as for anti-depressant drug discovery.

1. Introduction

Unipolar and bipolar depression (Table 1) are common and severely debilitating neuropsychiatric mood disorders (Boland and Alloy, 2013; Lee et al., 2012). Depression is not a 'one disease' state, and represents a spectrum of disorders with overlapping or shared symptoms (Nestler et al., 2002) (Fig. 1). Key symptoms of unipolar depression, also known as major depressive disorder (MDD), include low mood, anhedonia, fatigue and decreased attention (American Psychiatric Association, A.P.A., 2013) (Table 1). MDD affects ~17% of people throughout their lifetime, and has a significant impact on public health (Kessler et al., 2003). Bipolar depression (BD) manifests in alternating depression (low mood) and manic/hypomanic episodes (Table 1), and affects ~3% of US adults annually (Kessler et al., 2005).

Abbreviations: ACTH, adrenocorticotropic hormone; ATP, adenosine triphosphate; BD, bipolar depression; BDNF, brain derived neurotrophic factor; BP, bipolar disorder; CMUS, chronic mild unpredictable stress; CUS, chronic unpredictable stress; CRH, corticotropin releasing hormone; DAT, dopamine transporter; CSF, cerebrospinal fluid; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; GABA, gamma-aminobutyric acid; GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal (axis); HPI, hypothalamic–pituitary–interrenal (axis); HTS, high-throughput screens; IL, interleukins; MAOI, monoamine oxidase inhibitor; MCP-1, monocyte chemotactic protein-1; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate; NPY, neuropeptide Y; PCP, phencyclidine; PPCA, trans-2-phenylcyclopropylamine; POMC, proopiomelanocortin; SERT, serotonin transporter; SNP, single nucleotide polymorphism; SS, serotonin syndrome; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TNF, tumor necrosis factor.

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Translational animal models, especially rodent tests, have long been a useful tool for studying depression pathogenesis (Porsolt et al., 1978) (Table 2). However, they are limited by high cost and are relatively low throughput. For example, the housing of laboratory rodents and their chronic drug treatment can be both expensive and time-consuming. Additionally, a long gestation period and small litters lengthen genetic or developmental studies using these species. Furthermore, some models of MDD, such as chronic unpredictable stress (CUS, Table 2), are not only expensive and raise bioethical concerns in mammals, but also often lead to difficulty in replicability (due to different handling procedures) between or within different laboratories (Murison and Hansen, 2001). Therefore, the use of complementary models can foster future research into the pathophysiology of depression.

Due to their high throughput value, genetic tractability, high physiological homology to humans, low cost and quick reproductive cycle, zebrafish (*Danio rerio*) have emerged as a promising new model species for studying various brain disorders (Jesuthasan, 2012; Nguyen et al., 2013a; Stewart et al., 2014). Because zebrafish offer an important 'evolutionary' perspective on neuropsychiatric disorders and their conserved, core underlying mechanism (Kalueff et al., 2014; Stewart et al., 2010), zebrafish can represent a useful model for studying CNS disorders. Here, we discuss the current state of utilizing zebrafish to study depression, and outline further directions of investigation (using this model organism) to understand pathogenesis and develop innovative therapeutic approaches for this disorder.

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Table 1
Main depressive disorders as outlined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (American Psychiatric Association, A.P.A., 2013).

Disorders	Diagnostic criteria summary
Bipolar and related disorders	
Bipolar I disorders	Bipolar disorder with at least 1 manic or mixed episode
Bipolar II disorders	Bipolar disorder with at least 1 hypomanic episode and one episode of MDD
Cyclothymic disorder	Long term (>2 years) mood disorder that is a mild form of bipolar disorder
Substance/medication-induced bipolar and related disorder	Bipolar disorder directly resulting from substance abuse
Other specified and unspecified bipolar and related disorders	Diagnosis for bipolar disorder characteristics which do not fall into otherwise specified BD types
Depressive disorders	
Disruptive mood dysregulation disorder	Juvenile and adolescent condition in which tantrums, outbursts, and irritability are frequent
Major depressive disorder (MDD), single and recurrent episodes	Feelings of sadness, despair, anhedonia are persistent for long periods of time and interfere with quality of life
Persistent depressive disorder (dysthymia)	Chronic state of depression (>2 years), milder than MDD
Premenstrual dysphoric disorder	Feelings of depression, lethargy, anhedonia and irritability before menses (and ceasing after menses)
Substance/medication-induced depressive disorder	Depressive disorder resulting directly from substance abuse
Depressive disorder due to another medical condition	Depressive disorder secondary to a preexisting medical condition
Other specified and unspecified depressive disorders	Diagnosis for depressive disorders which do not fall into other categories of depressive disorders

2. Clinical mood disorders

2.1. Major depression

MDD is a complex disorder with both genetic and environmental causes (Rutter, 2003; Venzala et al., 2013), as well as complex gene–environment interactions (Eaves et al., 2003; McClearn, 2002) reported for various CNS genes (e.g., encoding brain-derived neurotrophic factor (BDNF), corticotropin releasing hormone (CRH) or leptin; Krishnan and Nestler, 2008; Onishchenko et al., 2008). MDD is neurochemically mediated (MacQueen and Frodl, 2011; Owens and Nemeroff, 1994), as brain catecholamines (serotonin, dopamine and norepinephrine), glutamate and gamma-aminobutyric acid (GABA) are strongly implicated in MDD (Kalueff and Nutt, 2007; Maas, 1979; Niciu et al., 2013; Nutt, 2008; Plante et al., 2012). Pharmacologically modulating MDD, the most common clinically used antidepressants include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (Offidani et al., 2013; Schwartz, 2013; Syed et al., 2013). In line with this, polymorphisms in the dopamine transporter (DAT) (Haeffel et al., 2008) and serotonin transporter (SERT) genes have been linked to a high incidence of MDD (Ogilvie et al., 1996; Risch et al., 2009), whereas targeting SERT by SSRIs remains the most effective pharmacological treatments of MDD (Hernandez et al., 2013).

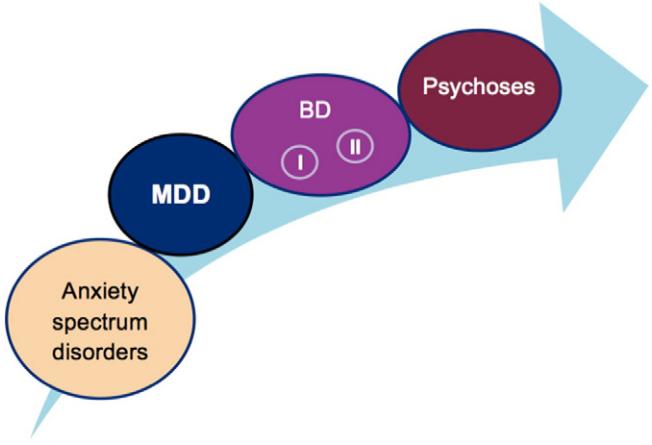

Fig. 1. Spectrum nature of mood disorders (MDD — unipolar, major depressive disorder; BP — bipolar disorder, including types I and II; see Table 1 for diagnostic criteria summary). Depression is not a 'one disease' state, and represents a spectrum of disorders with overlapping or shared symptoms, with potential comorbidity extending from anxiety to serious psychological disturbance (e.g., suicidal ideation).

MDD is characterized by several symptoms, including depressed mood, anhedonia, weight fluctuation, insomnia, agitation, fatigue, feelings of worthlessness, lack of concentration and suicidal ideation (American Psychiatric Association, A.P.A., 2013). This disorder has strong genetic and environmental causes, also showing high comorbidity with other psychiatric disorders (Ehlers et al., 1988; McDonald et al., 2003; Regier et al., 1998) (Table 1). In humans, MDD typically presents during adolescence, with females showing an earlier onset than males (Eley and Stevenson, 1999; Lewinsohn et al., 1994). Children of depressed parents are also more likely to have MDD (Weissman et al., 1987), and nearly 90% of individuals with MDD have recurrent episodes (Kennedy, 2008). Various other factors that predispose one to, or exacerbate MDD, include obesity, low activity, childhood adversity and traumatic experience (Blumenthal et al., 2007; Carpenter et al., 2000; Morina et al., 2013; Tunnard et al., 2014). In addition to MDD, other sub-types of depression include disruptive mood regulation disorder, persistent depressive disorder, and premenstrual dysphoric disorder, as well as substance/medication induced depressive disorders (Table 1) (American Psychiatric Association, A.P.A., 2013). MDD is frequently comorbid with other mental disorders, such as anxiety spectrum disorders, personality disorder, addiction and drug abuse (Iketani et al., 2002; Regier et al., 1990).

Abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis are also associated with MDD (Nestler et al., 2002), and may be corrected by SSRI therapy (Hernandez et al., 2013). Furthermore, depressed individuals exhibit higher levels of stress-associated hormones (e.g., cortisol) (Bhagwagar et al., 2005; Brown et al., 2004) and pro-inflammatory cytokines, as well as reduced levels of anti-inflammatory cytokines (Miller et al., 2009; Sutcigil et al., 2007).

2.2. Bipolar disorder

BD is associated with alternating depressed and manic/hypomanic states (American Psychiatric Association, A.P.A., 2013) (Table 1). Bipolar I disorder (BDI) is defined as 1 or more manic episodes or mixed episodes, whereas bipolar II disorder (BDII) has 1 hypomanic episode with one or more major depressive episodes (American Psychiatric Association, A.P.A., 2013). BD not otherwise specified (BDNOS) occurs when an individual has abnormal bipolar symptoms which do not fit in bipolar I or II disorder, whereas cyclothymia represents a mild, long term (>2 years) form of BD (American Psychiatric Association, A.P.A., 2013). BD is frequently comorbid with schizophrenia, MDD, anxiety disorders, drug abuse and various other psychiatric disorders (Buckley et al., 2009; Hwu et al., 1996; Krishnan, 2005; Strakowski et al., 1998) (Fig. 1). Risk factors for BD include obesity, smoking, drug abuse, and poor diet (McIntyre et al., 2004). Like MDD, BD is also rooted in genetics and environmental factors (Lichtenstein et al., 2009; Strober et al.,

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