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Zebrafish and conditioned place preference: A translational model of drug reward

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ABSTRACT

Addiction and substance abuse are found ubiquitously throughout human society. In the United States, these disorders are responsible for amassing hundreds of billions of dollars in annual costs associated with healthcare, crime and lost productivity. Efficacious treatments remain few in number, the development of which will be facilitated by comprehension of environmental, genetic, pharmacological and neurobiological mechanisms implicated in the pathogenesis of addiction. Animal models such as the zebrafish (*Danio rerio*) have gained momentum within various domains of translational research, and as a model of complex brain disorders (e.g., drug abuse). Behavioral quantification within the conditioned place preference (CPP) paradigm serves as a measure of the rewarding qualities of a given substance. If the animal develops an increase in preference for the drug paired environment, it is inferred that the drug has positive-reinforcing properties. This paper discusses the utility of the zebrafish model in conjunction with the CPP paradigm and reports CPP behavior following acute exposure to 0.0%, 0.25%, 0.50%, and 1.00% alcohol, and 0 mg/L, 50 mg/L, 100 mg/L and 150 mg/L caffeine.

1. Introduction

Substance abuse and addiction are complex brain disorders found ubiquitously throughout human society; they not only cause tremendous harm to the user, but are estimated to amass hundreds of billions of dollars annually in costs associated with health care, crime, and lost productivity, solely within the United States (National Institute on Drug Abuse [NIDA], 2010). Alcohol is a particularly devastating substance; it's the third largest risk factor for disease in the world and is responsible for ~2.5 million deaths annually (World Health Organization [WHO], 2011). Globally, the annual use of alcohol is estimated to be eight times higher than the annual prevalence of illicit drug use (UNODC World Drug Report, 2012). Caffeine, a less harmful substance than alcohol, does not meet the criteria necessary to elicit substance abuse according to the DSM-V, albeit it's the most commonly used drug in the world (Winston, 2005) with over 85% of people consuming it regularly (American Psychiatric Association, 2013).

Efficacious treatments for substance abuse remain few in number. Development of novel pharmacotherapies and prevention/intervention strategies will be facilitated by comprehension of environmental, genetic, pharmacological and neurobiological mechanisms implicated in the pathogenesis of addiction. Animal models have been utilized to help elucidate such mechanisms and processes, particularly those associated with the experience of reward. Organism survival is often dependent upon learning the conditions necessary to acquire naturally rewarding and reinforcing stimuli that serve homeostatic and reproductive purposes (Hyman et al., 2006). Animals rapidly learn the behavioral responses necessary to obtain natural rewards (e.g., food or sex) and the environmental cues that predict them (Bell et al., 2010; Lau et al., 2006). Learning also occurs following consumption of rewarding psychoactive substances (Everitt et al., 2001; Hyman et al., 2006). Rapid conditioning occurs when drug use is paired with a place, thing, or emotional state, primarily due to the integrated nature of reward circuitry with the memory, motivational, and emotional centers of the limbic system (McLellan et al., 2000). Exposure to the aforementioned stimuli may induce craving for the drug in individuals that are dependent on a substance, and even in those who have been abstinent from drug use for a period of time (Childress et al., 1999). These Pavlovian and operant learning processes are believed to mediate transitions from casual, voluntary drug use, to more habitual and compulsive behaviors (Alderson et al., 2000; Everitt and Robbins, 2005). Understanding how such factors contribute to drug seeking behaviors

Abbreviations: NIDA, national institute on drug abuse; WHO, world health organization; UNODC, united nations office of drugs and crime; DSM-V, diagnostic and statistical manual of mental health disorders, fifth edition; ZND, zebrafish neurophenome database; CNS, central nervous system; GABA, gamma-aminobutyric acid; CPP, conditioned place preference; CPA, conditioned place aversion; IP, intraperitoneal; IM, intramuscular; UCS, unconditioned stimulus; CS, conditioned stimulus; ANOVA, analysis of variance; VTA, ventral tegmental area; NAc, nucleus accumbens; PFC, prefrontal cortex; BAC, blood alcohol concentration.

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may facilitate new treatment strategies. Rats and mice have been conventionally employed in this endeavor, chiefly due to the anatomical, biological, and genomic homology between rodents and humans (Lieschke and Currie, 2007). However, utility of rodent models are burdened by challenging husbandry, difficult in utero manipulation, and are unamenable to high-throughput screening. The zebrafish (*Danio rerio*) provides an opportunity to overcome these limitations.

2. Zebrafish

The upsurge in popularity of the zebrafish model over the past several decades has been profound, particularly in the fields of genetics, developmental biology and behavioral neuroscience. Zebrafish husbandry and facility maintenance are simple and economical, large numbers of animals can be housed in relatively small areas, and robust behavioral phenotypes can be studied and manipulated in both larvae and adults. Many disadvantages of the rodent model are rectified by the aforementioned characteristics of zebrafish, providing researchers with a model amenable to embryonic manipulation and high-throughput screening of genetic mutations and pharmacological agents (Bang et al., 2002; Burns et al., 2005; Gerlai, 2010; Kokel et al., 2010; Rihel et al., 2010) Zebrafish are particularly well-suited for such large-scale screens, primarily due to prolific breeding that produces large numbers of rapidly developing progeny. Sequencing of the zebrafish genome has recently been completed, and ~70% of human genes were found to have at least one zebrafish orthologue (D.G. Howe et al., 2013; K. Howe et al., 2013). Thus, this species may be ideally suited as a vertebrate model for use in preclinical drug evaluation of small molecules and the investigation of genetic mechanisms, which often entails the screening of thousands of mutants (Burns et al., 2005; Gerlai, 2010; Lockwood et al., 2004).

Sophisticated video-tracking technologies have recently been adopted in zebrafish neurobehavioral research capable of automated quantification and analyses of numerous behavioral parameters, such as distance traveled, average velocity, angular velocity and turning angle, in both single and multiple fish across numerous paradigms (Cachat et al., 2011). Three-dimensional spatiotemporal swim patterns may also be constructed by utilizing multiple cameras and computer software (Cachat et al., 2011, 2013). Valuable tools such as these reduce personnel time, eliminate observer bias, and permit researchers to accurately and exhaustively dissect zebrafish behavior.

Investigators are also aided by several publicly accessible databases, which increase dissemination of published findings in the field of zebrafish neurobehavioral research. The Zebrafish Neurophenome Database (ZND; http://www.tulane.edu/~znpindex/search) is a comprehensive open-access collection of adult and larval zebrafish behavioral and physiological data from laboratories throughout the world (Kyzar et al., 2012a; Zapolsky et al., 2012). The ZND categorizes experimental information including, but not limited to, primary investigator, zebrafish strain/sex/age/quantity, drug and dosage, duration of treatment, delivery method, behavioral paradigm, positive/negative findings, affected/unaffected endpoints, and statistical results. The Zebrafish Information Network (ZFIN; http://www.zfin.org) is another community resource and online database, consisting primarily of genetic, genomic and developmental data (D.G. Howe et al., 2013; Sprague et al., 2003). Bioinformatic databases such as these are invaluable tools for organizing and disseminating knowledge throughout the scientific community. Additionally, a comprehensive glossary consisting of 190 detailed zebrafish behaviors has recently been compiled, satisfying the necessity for consistent and well-defined terminology in the field (Kalueff et al., 2013).

The burgeoning zebrafish field is augmented by the vast data accumulated from the rodent model; indeed, many behavioral paradigms utilized in rodent research have been aquatically converted to accommodate the zebrafish, including the open field, light–dark, T-maze, social preference, and predator avoidance tests (Barba-Escobedo and Gould, 2012; Cachat et al., 2013; Kyzar et al., 2012b; Gerlai et al., 2006; Grossman et al., 2010). Facilitated by such paradigms, the zebrafish has emerged as a promising vertebrate model for human brain disorders, e.g., addiction (Stewart et al., 2010, 2011). Although there is morphological disparity between zebrafish and humans, comparable features of the central nervous system (CNS) allow for results to be generalized to mammals (Guo, 2009). For instance, albeit the nucleus accumbens and ventral tegmental area have yet to be identified in zebrafish, dopaminergic projections to the zebrafish forebrain are believed to parallel the mesolimbic dopamine system in mammals, which is hypothesized to mediate the neurobiology of reward and reinforcement (Rink and Wullimann, 2002a, 2002b). In mammals, the hippocampus is largely responsible for spatial memory, and although zebrafish lack this region, the lateral pallium is believed to be structurally homologous, suggesting a conservation of some cognitive processes (Tropepe and Sive, 2003). Furthermore, the zebrafish CNS uses many neurotransmitters found in mammals, including GABA, glutamate, dopamine, norepinephrine, serotonin, histamine, and acetylcholine (Panula et al., 2010). Although the zebrafish CNS is more simplistic than its mammalian counterpart, it is capable of mediating complex behaviors such as associative learning, and most notably, addiction (Mathur et al., 2011a; Ninkovic and Bally-Cuif, 2006; Sison and Gerlai, 2010).

Drugs of abuse are observed to induce tolerance, withdrawal, and place preference in both larval and adult zebrafish (Cachat et al., 2010a; Stewart et al., 2011; Tran and Gerlai, 2013). Anxiogenic phenotypes have been reported in adult zebrafish chronically exposed to 0.3% v/v ethanol, 72 mg/L diazepam, and morphine (1.5 mg/L single withdrawal, 1.0 mg/L repeated withdrawal) and then exposed to fresh water (Cachat et al., 2010a). Ethanol and morphine withdrawal were also found to significantly increase whole-body cortisol levels. These results are comparable to the effects of withdrawal on rodent measures of behavior and physiology (Almela et al., 2012; Silva and Madeira, 2012), indicating good face and construct validity (Hyman et al., 2006). The translational relevance of zebrafish allows for high-throughput in-vivo screening of pharmacologically manipulated behavioral phenotypes involved in addiction and reward seeking behavior. In this regard, researchers are beginning to capitalize on the advantageous characteristics of this model, facilitated by a well-established experimental paradigm for evaluating the abuse potential and rewarding (or aversive) properties of drugs and natural rewards.

3. The conditioned place preference paradigm

A recent query in PubMed with search terms, 'conditioned place preference (CPP) or conditioned place aversion' yielded 3176 publications dating back to 1974. A common alternative to drug self-administration, CPP has been extensively utilized, primarily with rodents, to evaluate rewarding effects of psychoactive compounds (Tzschentke, 1998, 2007). CPP has been induced in rodents by addictive substances frequently abused by humans, including D-amphetamine (Yates et al., 2012), cocaine (Bahi et al., 2008; Russo et al., 2008), diazepam (Papp et al., 2002), ethanol (Kotlinska et al., 2011), heroin (Braida et al., 2001), ketamine (Li et al., 2008), methamphetamine (Zakharova et al., 2009), morphine (Liang et al., 2006), and nicotine (Brielmaier et al., 2008). The literature reveals that CPP has not been established with drugs that humans don't typically abuse, such as antidepressants, neuroleptics, and antihistamines (Papp et al., 2002). Furthermore, drugs that do elicit self-administration by human addicts are also found to be self-administered by animal models (O'Brien and Gardner, 2005). In contrast with self-administration behaviors, CPP has been found to differentially assess drug reward and engage distinct neuropharmacological circuitry (Tzschentke, 1998).

Similar to many rodent behavioral paradigms, CPP has been adopted in zebrafish neurobehavioral research (Darland and Dowling, 2001; Mathur et al., 2011b; Ninkovic and Bally-Cuif, 2006; Parmar et al.,