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Review

The crayfish model (*Orconectes rusticus*), epigenetics and drug addiction research

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ABSTRACT

Fundamental signs of epigenetic effects are variations in the expression of genes or phenotypic traits among isogenic mates. Therefore, genetically identical animals are in high demand for epigenetic research. There are many genetically identical animals, including natural parthenogens and inbred laboratory lineages or clones. However, most parthenogenetic animal taxa are very small in combined epigenetic and drug addiction research. *Orconectes rusticus* has a unique phylogenetic position, with 2–3 years of life span, which undergoes metamorphosis that creates developmental stages with distinctly different morphologies, unique lifestyles, and broad behavioral traits, even among isogenic mates reared in the same environment offer novel inroads for epigenetics studies. Moreover, the establishment of crayfish as a novel system for drug addiction with evidence of an automated, operant self-administration and conditioned-reward, withdrawal, reinstatement of the conditioned drug-induced reward sets the stage to investigate epigenetic mechanisms of drug addiction. We discuss behavioral, pharmacological and molecular findings from laboratory studies that document a broad spectrum of molecular and, behavioral evidence including potential hypotheses that can be tested with the crayfish model for epigenetic study in drug addiction research.

1. Introduction

The nervous system of crayfish is not very complex when compared with that of humans. While the brain of a human has an estimated billions of neurons, that of crayfish has only about 120,000 estimated neurons (Kagaya and Takahata, 2010). The simplified nervous system in crayfish makes it a unique model system for scientific research. The crayfish nervous system has been thoroughly mapped; it has large neurons approximately 40 times larger than the size of a human neuron (Liu and Herberholz, 2010), of which 30–35 neurons are dopaminergic and 25–30 of the dopamine neurons are located in the suboesophageal ganglion (Tierney, 2003). The neuronal wiring in the nervous system of crayfish is well known, such that the precise target of a pharmacological or molecular manipulation can be determined. The simplicity of the crayfish nervous system and the detailed knowledge about drug-induced behavioral plasticity indicate a novel system with several opportunities to explore the activities of the well-known monoamine neuromodulatory systems (dopamine neurotransmitter) associated with actions of mammalian drugs of abuse. The fundamental question relevant to the current review is; what exactly does crayfish epigenetics mean to drug addiction research? It means that we could use crayfish to identify the conserved epigenetic elements of natural aspects of addiction in an evolutionary distant species. In fact, we can use the simplicity of the nervous system of crayfish as a tool to understand the unknown mechanisms of DNA or histone methylation in drug addiction research. Doing so could help tease out the specific relationships between behavior, nervous system function and identifying epigenetic mechanisms that could provide clues for research in humans. Our initial focus is to develop concepts and hypotheses that can be tested in the laboratory to determine the detailed epigenetic aspects of drug addiction in crayfish. We hope that the simplified crayfish nervous system and behavior can aid in answering some complex epigenetic questions in drug addiction. Once these questions are addressed in the crayfish model, it may provide clues into the mammalian complex systems. In this review, we first briefly discuss epigenetics and related mechanisms including application in drug addiction research. Second, we discuss stochastic development and environmental effects including how epigenetic mechanisms induce particular phenotypes. Third, we highlight

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how metamorphosis is associated with diet-induced epigenetic transcriptional reprogramming modulated by histone modification. Next, we discuss the potentials of the crayfish model in epigenetic research in drug-induced reinstatement of drug seeking behavior. Thereafter, we discuss epigenetic mechanisms and propose different hypotheses to test how specific epigenetic mechanisms may modulate drug-induced reward and re-instatement. We conclude by proposing hypotheses that can be tested in crayfish for epigenetic mechanisms in drug addiction research.

2. The crayfish model in drug addiction research

Crayfish, honey bees, fruit flies, nematodes, and several other invertebrates display strong responses to drugs of abuse and their natural reward circuits are reported to be sensitive to human drugs of abuse. In general, invertebrates and vertebrate systems for drug addiction including humans share similar neurotransmitter systems with homologous receptors, and common pathways underlying drug addiction (Porzgen et al., 2001). The underlying mechanisms are strongly conserved throughout metazoan evolution, and invertebrate models have recently emerged as powerful new study systems in addiction research, offering a comparative approach. The worth of crayfish as a model system for studies of addiction was not previously recognized because a drug-reward phenomenon had not been documented as well as evidence of conditioned and unconditioned effects of drugs of abuse. In principle, an ideal model system for drug addiction should show evidence of positive reinforcing properties for drugs, compulsive patterns of drug use, withdrawal symptoms, and possess large and recognizable neurons that are amenable to detailed epigenetic, neurophysiological and neuropharmacological manipulations. However, in a series of behavioral, molecular and pharmacological studies, we demonstrate that the crayfish natural reward system is sensitive to human drugs (Imeh-Nathaniel et al., 2014; Nathaniel et al., 2012a; Panksepp et al., 2004). Moreover, we provide evidence of drug-induced reinstatement of drug seeking behaviors (Datta et al., 2018; Nathaniel et al., 2012a; Nathaniel et al., 2009). We demonstrate that crayfish are capable of exhibiting conditioned place preference for environments in which they received cocaine, morphine or amphetamine and can exhibit withdrawal symptoms (Nathaniel et al., 2009). Our initial findings generate a novel system with a demonstrated complement of positive reinforcing properties for drugs of abuse, and the presence of withdrawal symptoms. However, this previous success does not yet lead to the generation of a multifaceted robust experimental model for exploring the underlying neural mechanisms of drug addiction. Rather, it highlights the demand to develop more experiments to immediately characterize other substrates of addiction in the crayfish system. Moreover, it provides an opportunity to investigate the epigenetic basis of brain function and plasticity associated with drugs of abuse in an invertebrate model with an established evidence of response to drugs of abuse.

3. Epigenetics; differences in the expression of genes without a change of the DNA sequence

In 1942, an embryologist and theoretical biologist, Conrad Waddington introduced ‘epigenetics’ as a new terminology in relationship with “epigenesis”, which is described as the developmental processes between the genotype and phenotype (Deichmann, 2016). Epigenetics was originally applied to single-celled organisms that reproduced by simple cell division and was later applied to cell lineages. In subsequent years, the need to understand processes associated with genetic regulation in the development of higher organisms broadened epigenetics mechanisms to focus on chemical or structural alterations of chromatin i.e. complexes of DNA and proteins into which the genomes of higher organisms are parceled. Therefore, the application of epigenetics to developmental and experiential processes in higher organisms was a natural extension of the initial idea. In general, epigenetic changes are now part of the mechanisms for the regulation of gene expression in complex organism.

Epigenetics is well known for providing a deeper understanding of the modifications in gene expression that are transmitted from generations to generations and occurring without an alteration in DNA sequence (Heinbockel and Csoka, 2018). The observed differences in the expression of heritable genes occur not because of changes in DNA sequence, but due to modification of chromatin facilitated by environmental factors (Skvortsova et al., 2018). It is known that epigenetics mechanism control transcription processes and gene expression (Heinbockel and Csoka, 2018). This highlights of how epigenetics provides the platform to understand the translational effect of drug of abuse disorders, and how they can be treated using different means including pharmacotherapeutic tools. Moreover, epigenetic changes in response to experience and environmental challenges represent the mechanism that facilitates long-term changes in cellular, physiological, and behavioral phenotypes that may underlie different aspects of drug addiction (Borish, 2016; Lee, 2016; Moore, 2017) (Feng, 2017; Wong et al., 2011; Zwiller, 2015).

An important mechanism associated with epigenetic alteration is variation in DNA methylation which is linked to environmental factors (Garg et al., 2018; Otto et al., 2018). In general, DNA methylation and alterations have been extensively investigated (Perez et al., 2019; Weaver et al., 2019), especially in different clinical conditions such as cancer (Liu et al., 2019; Parbin et al., 2019), hypertension (Stoll et al., 2018), stroke (Kassis et al., 2017; Narne et al., 2017) and drug addiction (Berkel and Pandey, 2017; Brown and Feng, 2017; Cadet et al., 2016; Zwiller, 2015). In the functioning of DNA methylation, there is a multifaceted interaction between DNA methylation and histone modification (Rose and Klose, 2014). Therefore, histone modification is another well studied epigenetic alteration which may result in transcriptional repression or activation in different models of drug addiction. It is important to point out that histone alteration or modification includes different types of posttranslational changes such as acetylation and methylation, which have very different effects on transcriptional activity (Daskalaki et al., 2018; Gonzalez et al., 2018b; Mosquera et al., 2019; Nevitt et al., 2018). While histone acetylation results in transcriptional activation, histone methylation can result in either transcriptional activation or repression, and this depends on the site of methylation.

The relationship between DNA methylation and histone lysine methylation is of particular interest because the two are highly interconnected. It is known that the altered state and sequence of DNA can influence the methylation states on associated histones in chromatin, while the histone lysine methylation state of chromatin can as well affect the alteration of the DNA (Rose and Klose, 2014). For example, histone methylation may facilitate the recruitment of DNA methylation to some genomic regions and may exclude it in some regions as well (Chistiakov et al., 2017). In general, DNA and histone lysine methylation systems are tightly connected and rely mechanistically on each other for the normal functioning of chromatin function in vivo. While histone methylation is conserved among eukaryotes, the evolution of DNA methylation is thought to be complex but has been reported in invertebrates (Fraune et al., 2016; Hawes et al., 2018; Roberts and Gavery, 2012; Schulz et al., 2018), vertebrates (Champagne, 2013; Hanson et al., 2011; Hawes et al., 2018; Herbeck et al., 2017; McGowan et al., 2010) and in drug addiction research (Anier et al., 2018; Gonzalez et al., 2018a; Imperio et al., 2018; Jayanthi et al., 2018). In rats, withdrawal behaviors and cue-induced cocaine seeking were associated with DNA methylation alterations that correlated with gene expression changes (Jayanthi et al., 2018). This provides evidence for the reprograming of genes in specific brain regions following cocaine withdrawal resulting in the adjustment of epigenetic mechanisms by different drugs of abuse. In this context, epigenetic marks such as DNA methylation may act as regulators of genes such that they can be activated or deactivated by drugs inhibiting DNA methylation and

removing methyl marks from these genes. However, several lines of evidence indicate that DNA methylation affects genes already silenced by other mechanisms including histone hypoacetylation and methylation that contribute to the stabilization of the inactivation (Bannister and Kouzarides, 2011; Sadakierska-Chudy and Filip, 2015). Studies that ranged from mammals to yeast indicate that the histone acetylation and DNA methylation state is closely linked to transcription, and that histone modification is a dynamic process associated with transformational change in invertebrates and vertebrates. Two families of enzymes that are evolutionary conserved including histone acetyltransferases (HATs) and histone deacetylases (HDACs) mediate this property of histones. Although it is not clear whether specific histone modification states are heritable, there are cross-talks between histone modification, DNA methylation and even post-transcriptional regulation and this helps to strengthen and preserve the effects of histone-based epigenetic mechanisms in model systems. Drugs of abuse can alter epigenetic mechanisms and potentially interfere with histone acetylation in humans (Lotsch et al., 2013). Therefore, the need for alternative and low-cost whole-animal model system has given crayfish and other arthropods a chance for the investigation of trans-generational effects; identifying the epigenetic transmission of gene regulation states in drug treated conditions.

4. Epigenetics, stochastic development and environmental effects

Attempts to integrate epigenetics into evolutionary discussion are focused on environmentally facilitated epigenetic changes. It is also possible that genetic variants that do not alter the mean phenotype could modify the variation in particular phenotypes and this could be epigenetically modulated. This would represent an inherited stochastic variation that could explain the role of epigenetics phenotypic variation, including the inexplicable heritable genetic variation underlying a complicated disease such as drug addiction. A direct evidence of stochastic epigenetic variation suggests variation in DNA-methylated regions in mouse and humans directly linked to development and morphogenesis (Feinberg and Irizarry, 2010). This finding indicates that developmental and environmental influence on behavioral changes can be modulated by epigenetic mechanisms including DNA methylation and histone modifications (Feinberg, 2014). Moreover, a genetically inherited stochastic variation in evolution (Furrow et al., 2011), suggests that it provides the mechanism for the observed evolutionary adaptation in a dynamic environment that can be modulated epigenetically (Carja and Feldman, 2012), and increases susceptibility of a population with a dynamic environment to different diseases (Feinberg, 2014). Indeed, phenotypic variation is associated with epigenetic modifications in individuals either via developmental stochasticity or environmental effects (Vogt, 2015).

Stochastic development and environmental effects are two epigenetic phenomena that induce particular phenotypes, and both can blend to produce behavioral changes (Scheiner et al., 2017). Most of the observed behavioral traits in animals appear to differ due to stochastic variation, and this also depends on species (Vogt, 2015). Animals have sensitive windows for the predisposition to stochasticity and this depends on the trait and life history of the species (Feinberg, 2014). In general, embryonic development is significant in determinately growing vertebrates, while the adult life period is significant in indeterminately growing species such as crustaceans (Gartner, 2012). For example, differences in adult body size among inbred rats originates from stochasticity during the zygote and first cleavage stages (Gartner, 2012), while complete metamorphosis in crayfish creates developmental stages with unique and different morphologies, lifestyles with particular phenotypes at adulthood (Sargent and Lodge, 2014). While stochasticity-associated differences in ageing and drug use may have their embryonic origin and manifest even in the adulthood in humans (Feinberg, 2014), a sensitive time frame may also exist in crayfish (Spicer, 2001),specifically when drugs of abuse can alter the epigenetic programming such as DNA or histone methylation and subsequently change gene expression to induce behavioral changes. Moreover, laboratory and wild populations of crayfish are of the identical origin and monoclonal, making crayfish a unique animal model. In addition, crayfish produces large numbers of offspring that are genetically identical to the mother allowing extensive experimental manipulations to determine the relationships between genotype, epigenotype (i.e. stable patter of gene expression outside of the DNA sequence) and phenotype.

5. Epigenetics, drug-induced behavioral changes and metamorphosis

Evidence of cocaine-induced alterations in histone acetylation, phosphorylation and methylation in mice suggest that such modifications may regulate behavioral changes associated with cocaine-seeking behaviors in rats (Ploense et al., 2018), neuroadaptation associated with alcoholism in drosophila (Ramirez-Roman et al., 2018) and combined behavioral effects of nicotine and/or cocaine in rats (Hayase, 2017. Pharmacological or genetic manipulations of specific histone deacetylases (HDACs) in the nucleus accumbens (NAc) of drug treated rats reveal an in vivo alteration of histone acetylation resulting in behavioral sensitivity to cocaine (Malvaez et al., 2011). In the conditioned place preference test, drug-treated mice learned to associate the rewarding effects of cocaine with a novel environment (Hitchcock et al., 2019; Kennedy et al., 2013), while the systemic injection of HDAC inhibitors renders the rewarding effects of cocaine in mice treated with amphetamine and D1 agonists (Godino et al., 2015; Kalda and Zharkovsky, 2015; Kumar et al., 2005). These findings support the hypothesis that an increase in histone acetylation may potentiate behavioral changes associated with drugs of abuse. Since histone acetylation controls response to different environmental stimuli (Castino et al., 2018; Gonzalez et al., 2018b), we hypothesize pharmacological or genetic manipulations that result in an increase in histone acetylation may represent an epigenetic mechanism that regulates the respective behavioral responses. It is known that histone acetylation activities contribute to the process of gene activation, and there are different patterns of acetylation distinct and depends on the regulatory loci (Tian et al., 2005). Evidence indicates that differentiation events are facilitated by transformations in residue-specific histone acetylation at lineage-specific loci, and not on global histone acetylation events (Khilji et al., 2018). Whether it is cocaine, or other drugs; any pharmacological or genetic manipulations that result in an increase in histone acetylation represent an epigenetic mechanism that potentiates the respective behavioral responses.

Complete metamorphosis in crayfish creates developmental stages with markedly different morphologies and lifestyles, useful for investigating epigenetics and effects of early drug use. Metamorphosis exhibits phenotypic plasticity, including occurrence in two or more morphologically distinct phenotypes defined by the same genotype, such as larvae, pupae and young adults (Colgan et al., 2011; Simon et al., 2011). In such species, the different morphological stages (e.g. the larva, pupa and young adults) feed on different diets (Mukherjee et al., 2015). In this context, the development of larva to pupa or adult is associated with diet-induced epigenetic changes facilitated by histone modification resulting in changes of DNA methylation (Chittka and Chittka, 2010). The epigenetic mechanisms in crayfish may be controlled by diet, but other environmental stimuli maybe involved. In general, epigenetic mechanism is known to translate environmental stimuli into transcriptional reprogramming resulting in particular phenotypes (Mukherjee et al., 2015). Phenotypic plasticity in crayfish maybe controlled by epigenetic mechanisms such that pharmacological or environmental manipulations may produce distinct phenotypic variants. Therefore, phenotypic changes in invertebrates can be induced by a careful disruption of epigenetic mechanisms, e.g. HDAC and HAT inhibitors. These inhibitors are known to disrupt the rate of

metamorphosis in moth larvae, with HDAC causing the developmental clock to accelerate while HAT slowed down the developmental clock (Mukherjee et al., 2015). The unique developmental stages in crayfish may provide the opportunity to investigate the epigenetic and trans-generational effects of environmental factors including how diverse environmental stimuli exert potent and long-lasting changes in gene expression during conditioned or unconditioned behavioral changes in different drug-treated scenarios.

6. The crayfish model, epigenetic research in drug-induced reward and reinstatement

Our existing studies indicate that crayfish is a novel system for drug addiction research with evidence of sensitivity to psychostimulants, morphine withdrawal, reinstatement effects, and drug reward in a conditioned place preference paradigm. The Conditioned place preference paradigm is a behavioral paradigm that assesses the reinforcing properties of drugs of abuse (Wang et al., 2018). Since it depends mainly on the behavioral responses to a specific novel conditioned stimulus, it may only provide an indirect measure for the affective properties of drugs. A more direct approach that assesses the motivation to seek drugs, including the strength of associated reward maybe be better achieved using an operant behavior in a self-administration paradigm (King et al., 2017; Siciliano and Jones, 2017). In this approach, mammals are able to control the intake of drugs performing a learned, operant task, such that the completion of a successful task is associated with the delivery of a bolus of the drug (Borland et al., 2017; Wang et al., 2018). A recent study developed a novel system for automated drug self-administration in crayfish and determined whether amphetamine reward alters crayfish behavior in an operant conditioning paradigm (Datta et al., 2018). Crayfish demonstrates an automated enactment of a spatially conditional self-administration paradigm providing a comparative perspective of investigating drug-sensitive reward similar to an operant behavior in a self-administration paradigm in mammals. Therefore, existing studies provide evidence of self-administration of drugs, cue and drug-induced, reinstatement and drug seeking behaviors (Datta et al., 2018; Nathaniel et al., 2012a; Nathaniel et al., 2009).

In advancing the existing studies from an epigenetic standpoint, an important hypothesis to test is how epigenetic changes such as modifications in histone acetylation, phosphorylation and methylation are involved in reward or re-instatement of drug-induced behavioral changes in crayfish. The important goals in the epigenetic basis of drug addiction, especially the long-lasting components of addiction, are to: 1) discriminate the epigenetics changes in drug-induced reward, extinction and re-instatement of drug-induced behavioral changes and, 2) to identify the major players that are associated with epigenetics changes. In other words, which of the histone protein modifiers is/are most critical during epigenetic changes associated with drug-induced reward, extinction and re-instatement of drug-induced behavioral changes. For example, the effect of drug treatment on histone acetylation during drug-induced conditioning place preference, reward, extinction and re-instatement of reward in crayfish can be investigated. In rats, histone acetylation is highly regulated by HATs and HDACs, which promote gene activation and gene repression. Indeed, inhibitors of HDAC promote synaptic plasticity, alter locomotion and rewarding responses to cocaine (Kumar et al., 2005). The same kind of research could now also be done with crayfish where the methylation and demethylation machinery of epigenetics is relatively simple when compared to mammals. Moreover, histone modification which is an important epigenetic mechanism (Zhao and Garcia, 2015) is not yet investigated in any invertebrate model system of drug addiction. Deciphering the functions of histone modulation in a model system is important to provide evolutionary perspective to epigenetic mechanism. Moreover, understanding gene regulation via histone modification in an invertebrate system of a drug addiction will provide a cross-species understanding of how epigenetic mechanism responds, integrate, and translate diverse environmental stimuli into structural and behavioral changes. The availability of complete DNA methylomes for several organisms (Pelizzola and Ecker1, 2011) such as oyster, reveals the evolution and the epigenetic modulation of developmental processes (Riviere et al., 2017). In mammals, DNA methylomes is helpful in clarifying the evolutionary aspect of epigenetic signature and its distribution in major key genomic elements (Wang et al., 2014). In *Tribolium castaneum*, gene body methylation shows a negative correlation with gene expression levels (Song et al., 2017) similar to the methylome of *Drosophila melanogaster* (Raddatz et al., 2013). Similarly, the epigenetic programming has been investigated in the marbled crayfish (Gatzmann et al., 2018). Findings provide novel insights into gene body methylation and its potential role in the regulation of genes in a fresh water crayfish. The behavioral changes associated with drugs in crayfish provide the opportunity to investigate specific phenotypes during drug-induced reward, extinction and re-instatement of drug-induced behavioral changes. Moreover, histones and histone-derived enzymes including acetylases and deacetylases and four core histone proteins (H2A, H2B, H3 and H4) are expressed in circulating hemocytes of crayfish and other crustaceans (Barzotti et al., 2006; Liu and Soderhall, 2007; Philip et al., 2016; Rosa and Barracco, 2010). Activities of histone acetylases (HAT) and deacetylases (HDAC) can be used to determine how chromatin or histone acetylation are altered during, (1) extinction and (2) re-instatement of drug-induced behaviors in drug-treated crayfish. It is possible that HAT and HDAC activities may not only potentiate the effects of drug on gene histone acetylation, but also enhances the acquisition, extinction and reinstatement effects induced by injected drugs. Testing such a hypothesis will reveal whether epigenetic changes underlie drug learning such as conditioning, extinction or alterations in drug sensitization or tolerance.

With a reduced number of neurons that can consistently be recognized across subjects, crayfish offer an excellent preparation in which to identify, and characterize specific epigenetics mechanisms peculiar to reward or extinction or reinternment of drug induced behavioral changes. In this context, a crayfish model may thus serve as a contrastive filtering tool to identify critical common epigenetic players, including those with a higher probability of being the key players in addictive cascades. Therefore, conserved variables may offer an opportunity to identify these central components, providing useful targets for the development of future research into therapeutic interventions. The crayfish system will provide a cross-species model that can effectively complement investigations of mammalian systems. This is specifically useful in studying epigenetic mechanisms because they retain the ancestral neural reward circuit that is evolutionarily conserved with unique behavioral changes associated with drugs of abuse (Buric et al., 2013). In this context, the ability to reverse the epigenetic signature in an established invertebrate model of addiction would offer a fundamentally new approach for more research on drug-induced reward, extinction or maintenance of addiction from epigenetic perspective. This provides the opportunity to identify significant universal epigenetic players in drug addiction. For instance, identifying key genes with a higher likelihood of being the key actors to parse epigenetic mechanisms in drug addictive phenomena. Since epigenetic mechanisms are now proposed as potential avenues that could lead to new treatments for the long-term effects of drug addiction, the crayfish model may provide an opening to identify the major components that may provide potential targets for the development of future curative interventions for drug addiction. Therefore, the crayfish system is suitable to contribute to the topic of whether histone acetylation is regulated during drug-induced reward, extinction and reinstatement.

7. Investigating histone phosphorylation and chromatin modification in crayfish

In mammals, the mesocorticolimbic dopamine (DA) system is a

main circuitry pathway capable of undergoing important remodeling of the brain's reward circuitry after exposure to drugs of abuse. The system includes the nucleus accumbens that participates in the rewarding and reinforcing effects of drugs (Ouzir and Errami, 2016). Histone phosphorylation is known to modulate transcriptional activation observed on the promoters of immediate early genes such as c-fos following induction after cAMP induction in striatal neurons of rats (Cruz et al., 2015). In rats pretreated with an HDAC inhibitor before cocaine administration, phospho-acetylation at the c-fos promoter and the induction of c-fos mRNA was potentiated. In vertebrates, the interplay between histone phosphorylation and acetylation are known to occur only at certain genes including the immediate early genes in response to acute cocaine or other drugs (Renthal and Nestler, 2012).

In crayfish, we have characterized the context-specific alteration of c-fos mRNA expression in the accessory lobe of crayfish during drug-induced reward resulting in evidence of an anatomical substrate of reward in the nervous system of crayfish (Nathaniel et al., 2012b). We determined whether the expression of Fos could serve as a sensitive indicator of differential gene activation by morphine in the nervous system of crayfish. C-fos is known to be regulated by drugs and encode nuclear proteins that can, in turn, activate or repress the expression of other genes (Zhang et al., 2006). C-fos mRNA expression is known to be a marker for stimulus-elicited brain activity (Minatohara et al., 2016), and is more transient than Fos protein expression (Neisewander et al., 2000). For this reason, we used c-fos mRNA expression to examine induction of the *c-fos* gene, by examining whether changes in c-fos mRNA is associated with conditioned drug-seeking behavior. Precisely, we determined the role of c-fos expression and its potentials in the long-term alteration of neural functions that may affect reward. Following 3 days treatment of crayfish with 2.5 μg or 5 μg dose of morphine and measurement of reward using the CPP test, morphine increased c-fos expression (Fig. 1). As shown in the figure, an increase in c-fos mRNA expression was detected in the two doses (2.5 μg and 5.0 μg) treated brain samples but not in the two control brain samples without drug. The expression of c-fos was correlated with the reward response of morphine, indicating a role for c-fos in mediating the initial response to morphine. This initial finding suggests that potential epigenetic hypotheses in drug addiction can emerge from epigenetic aspect of drug addiction research in crayfish. Moreover, cFos (Shipley et al., 2017, Cdk5 (Jiang et al., 2014), BDNF (Kolosov et al., 2016), Cyclophilin A (Glazer et al., 2015) and FosB (Sarashina and Endo, 2006) which have been associated with behavioral and motoric changes in vertebrate (Nestler and Aghajanian, 1997), have been reported in crayfish. Therefore, homologous addiction genes in mammals also exist within the crayfish genome. With the eventual characterization of the crayfish genome, identified genes can be analyzed to evaluate a direct epigenetic change that occurs during drug-induced reward, extinction and re-instatement of drug induced behavioral changes.

Fig. 2 summarizes the proposed model for the mechanisms by which acute or chronic exposure to a drug of abuse alters the steady state levels of mRNAs and gene expression through chromatin regulatory mechanisms of drug-induced reward, withdrawal and re-instatement in crayfish. The model proposes how epigenetic mechanisms alter chromatin structure so that subsequent drug administration into the nervous system of crayfish will modulate cfos and other genes by priming or desensitizing due to epigenetic alterations induced by prior chronic drug challenge. In general, histone methylation is a novel target to study and understand how specific drugs regulate specific gene transcription and chromatin modifications. This is because histone modification is more than a reflection of gene expression and may facilitate gene priming. A good example is the acetylation of BDNF in rats within 24 h after there is extinction of cocaine (Kumar et al., 2005). In this particular case, the steady-state regulation of BDNF protein levels is not significantly clear until a week of cocaine withdrawal (Grimm et al., 2003). This is an example where histone acetylation on a gene promoter heralds the induction of gene expression supporting the possibility that, at least for a subset of genes, acetylation of histone may be associated with the priming of genes for an ensuing induction.

Apart from facilitating underlying stable changes in the steady-state levels of mRNA expression of certain genes, gene priming and desensitization is thought to alter the inducibility of many additional genes in response to some subsequent stimulus in the absence of changes in baseline expression levels (Robison and Nestler, 2011). This type of priming effect represents latent epigenetic changes that can contribute to the addicted state (Trivedi and Deth, 2015). For example, it has been shown that the priming and desensitization of genes occur when > 10% of genes whose transcription is acutely induced by cocaine are no longer induced by a cocaine injection following prior chronic challenge to the drug (Maze et al., 2010). Although the mechanisms underlying such gene desensitization and priming is not very clear; one possibility is that a subset of primed genes show reduced binding at their promoters in specific brain regions suggesting the involvement of specific epigenetic factors. In moving forward, a potential hypothesis is to determine chromatin mechanisms that are recruited by drug exposure to mediate gene priming, desensitization and to understand the detailed mechanisms that target those particular genes.

Even though significant success has been achieved in identifying chromatin modifications in a variety of in vivo model studies (Daugherty et al., 2017; Luo et al., 2017; Paauw et al., 2018), there are several questions that are yet to be addressed. For instance, it is not yet

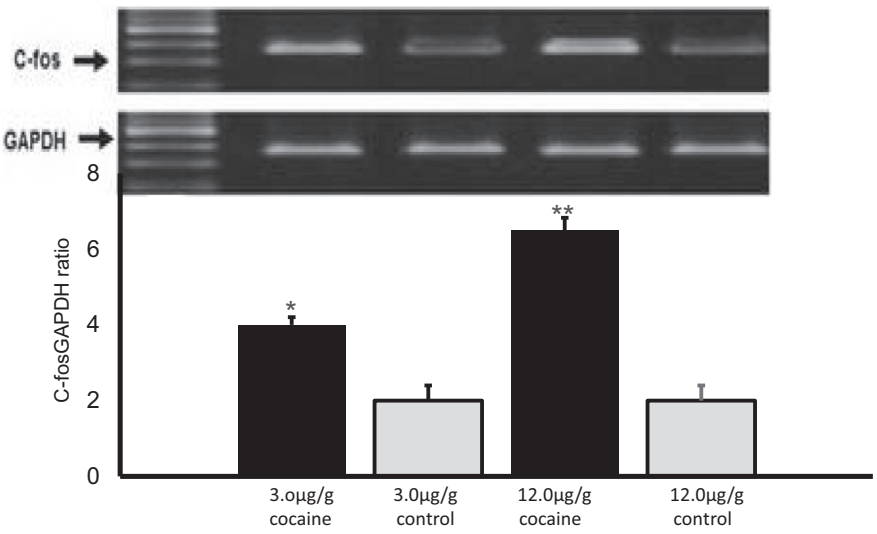

Fig. 1. C-Fos mRNA alterations in cocaine treated animals (3.0 μg and 12.0 μg/g) in a conditioned environment. The effect of cocaine on c-Fos mRNA expression was determined by quantitative RT-PCR (Top panel) and normalized with GAPDH (panel below). Data are expressed as mean ± S.E.M. at 35 min following conditioning after 5 days of cocaine injections (n = 9). Different doses of cocaine (3.0 μg/g and 12.0 μg/g) induced a significant [$F_{(3,27)} = 92.12$, $P < 0.001$] change in c-Fos mRNA expression in the conditioning treatment when compared with the control group. The expression of C-Fos mRNA was significantly higher at a higher.

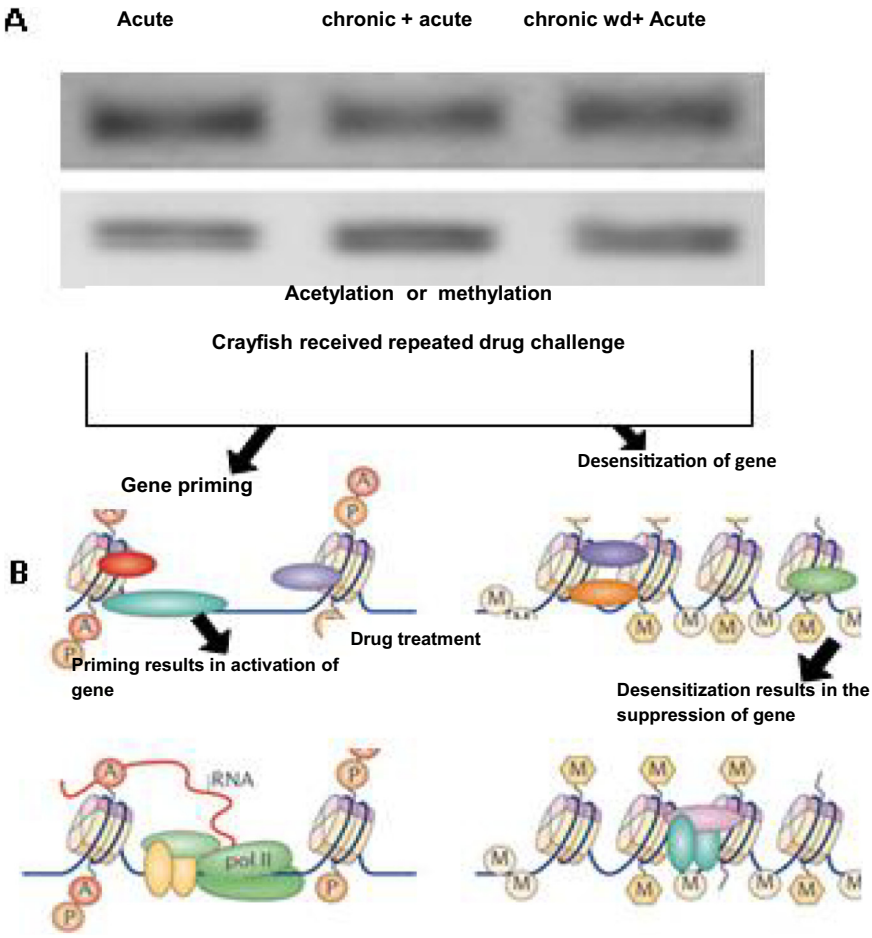

Fig. 2. Schematic illustration of gene priming and desensitization from drugs resulting in the regulation of a stable state expression of cfos and other genes including their inducibility while responding to other stimuli. In our previous study (Nathaniel et al., 2012b), the mrRNA in the panel (A) shows cfos genes expression following acute treatment (acute), chronic treatments, (chronic + acute), or following 5 days of withdrawal (wd) from chronic drug treatment (chronic wd + acute). In the panel (B), gene priming and desensitization are modulated by epigenetic mechanisms such that changes are hidden, suggesting that they are not shown by stable changes in the stable-state mRNA levels. Such changes alter chromatin structure so that subsequent drug administration into the nervous system of crayfish will modulate cfos and other genes by priming or desensitizing due to epigenetic alterations induced by prior chronic drug challenge. Investigating the mechanisms of histone acetylation and methylation in the promoter region of cFos, Cdk5, FosB and BDNF in the nervous system of crayfish during reward, extinction and re-instatement of drug-induced behavioral changes may provide clues on long-lasting changes in chromatin structure and behavior changes induced by drugs of abuse.

clear whether: 1) histone modifications are the primary cause of alterations in gene expression or whether they are just a mere reflection of changes in gene expression, 2) drug-induced histone effects on specific gene promoters are sufficient to alter the activity of a specific gene in vivo, and 3) such effects play a part in behavioral responses to drugs of abuse. Addressing these questions in rats and mice is challenging because most genetic and pharmacological tools manipulate chromatin structure genome-wide. This makes it difficult to establish a direct causal relationship between altered chromatin structure and observed transcriptional changes at a specific gene locus. These types of studies could be done with crayfish where the methylation and demethylation machinery are relatively simple when compared to mammals.

The simplicity in the neural system of crayfish model will provide the opportunity to directly target individual and specific identified drug-controlled genes such as cFos (Shipley et al., 2017), Cdk5 (Jiang et al., 2014), BDNF (Kolosov et al., 2016), Cyclophilin A (Glazer et al., 2015) and FosB (Sarashina and Endo, 2006) in crayfish, which have been reported in other crustaceans and are associated with drug-induced abnormal behavioral changes in vertebrates (Nestler and Aghajanian, 1997). This will allow comparison of the epigenetic signatures from which of these genes are permanently active, permanently silenced, periodically active and inactive, during reward, extinction or re-instatement, including the role of histone enzymes in on/off-switching of gene activity. Moreover, the crayfish can provide the opportunity to relate how epigenetic landscape can help to assess how gene-environmental interactions facilitate behavioral changes during reward, extinction or re-instatement after prolonged drug abstinence. The opportunity to manipulate histone activities at specific genes in a simple model is an excellent example of how to investigate drug-induced gene regulation beyond a perception of steady-state protein levels.

Since histone acetylation regulates transcriptional activity and contributes to drug induced alterations in gene expression and behavior (Renthal and Nestler, 2012), it is possible that drugs of abuse could induce alterations in the dopaminergic system and regulate histone acetylation in brain reward system of crayfish. A potential hypothesis to test is whether drug treatments are capable of inducing transcriptional changes by histone modifications in specific gene promoter regions of the c-fos, Cdk5, FosB and BDNF in brain reward system of the crayfish, and whether these events are associated with acquisition of place conditioning. Findings will reveal whether, 1) the effect of drugs induce short term histone acetylation and gene expression in the nervous system of crayfish during reward, 2) the changes is maintained for a long term during the withdrawal or drug reinstatement, 3) histone acetylation is associated with the persistently altered behavior after drug withdrawal or re-instatement,4) drug treatments regulate histone acetylation and methylation of the specific genes promoters involved in addictive features, and induces chromatic remodeling at specific genes, and regulate acetylation levels of H3 or H4 specific promoters (cFos, FosB, Cdk5 and BDNF) in the nervous system of crayfish. In this context, the simplified neural system in crayfish will provide an efficient tool to determine the specific individual impact of epigenetic mechanisms on the behavioral effects induced by intermittent drugs exposure during conditioning. This mechanism is yet to be fully understood even in mammalian models of drug addiction. Finally, the degree of changes in histone acetylation and gene or protein expression after drug withdrawal and re-instatement can be determined to show whether epigenetic mechanisms in an invertebrate model of drug addiction could provide clues on long-lasting changes in chromatin structure and behavior abnormalities induced by drugs of abuse.

8. Conclusion

We have previously developed robust behavioral paradigms for measures of reward strength associated with drugs of abuse, extinction and re-statement of drug-induced behavioral changes. In this review, we highlight findings from our previous studies and propose different hypotheses to be tested to study epigenetic mechanisms of drug-induced reward, extinction and re-instatement of reward in crayfish. With the eventual characterization of the crayfish genome, we anticipate being able to 1) construct crayfish microarrays to evaluate genetic changes that result from self-administration, 2) identify all the genes that control specific drug-induced changes in chromatin structure, and 3) determine how pharmacological or genetic manipulations of chromatin-remodeling enzymes are altered when crayfish self-administers drugs of abuse.

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