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Drug-sensitive Reward in Crayfish: Exploring the Neural Basis of Addiction with Automated Learning Paradigms

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ABSTRACT

Results of recent work from our labs and those of others have broadened perspectives on addiction beyond a human-specific, cognitive phenomenon. Addictive plant alkaloids are defensive compounds which have arisen to counter herbivory. With insects the true targets of the coevolutionary arms race, humans may be little more than collateral damage when impacted by 'human' drugs of abuse. The present paper summarizes recent contributions, with a primary focus on our own research in crayfish, where we characterize the behavioral and neural consequences resulting from chronic and acute exposure to psychostimulant and addictive drugs. Substituted phenethylamines, like amphetamine and cocaine, exhibit a wide range of effects in crayfish with direct parallels to those described from mammalian preparations. Unconditioned effects include intoxication and psychostimulation, where repeated exposure is accompanied by tolerance and sensitization, respectively. Psychostimulants exhibit powerful reinforcing properties in conditioned place preference, subject to extinction and reinstatement. Crayfish readily self-administer amphetamines using instrumental learning approaches. With a nervous system modular and uniquely accessible to neural probing, crayfish offer unique opportunities for studying the basic biological mechanisms of drug effects, for exploring how the appetitive disposition is implemented, and for examining how this is related to the rewarding action of drugs of abuse.

1. Introduction

Except in Louisianan culinary circles, crayfish are frequently underappreciated. This general lack of enthusiasm for decapod crustaceans likely stems from the fact that our phylogenetic histories diverged very early during the Precambrian era, more than 550 million years ago (Regier and Schultz, 1998). Given significant morphological, anatomical, and life-history differences, preclinical science has traditionally eschewed the use of invertebrate models, and has instead focused attention on a rather small number of mammalian preparations. As comparative research utilizing a broader array of model systems continues to generate significant insights into the basic neural mechanisms underlying behavior (and its disruption in disease states), this vertebrate-centric perspective of preclinical research is gradually eroding. The Nobel Prize in Physiology or Medicine has been awarded for work on invertebrates explaining the propagation of electrical impulses in neurons (squid, 1963), visual function in retina (horseshoe crab, 1967), the organization of social behavior (honeybee, 1973), genetic control of development (flies, 1993), associative learning (molluscs, 2000), neuronal cell death (nematodes, 2002), and the molecular mechanisms controlling circadian rhythms (flies, 2017). Clearly, invertebrate preparations offer a number of distinct experimental advantages for exploring fundamental mechanisms in neuroscience. At a structural level, functional homologies are implemented in highly modular nervous systems with significantly reduced complexity. For instance, the neuronal system of lobsters and crayfish comprises a relatively small number of neurons which, in comparison to vertebrates, are often exceptionally large and accessible to physiological characterization. The ability to approach questions at the single cell level is further aided by the fact that individual neurons, with the same specific morphology and cellular properties, can often be found across individuals (Heinrich et al., 1999; Hörner et al., 2002). Because of this, seminal work has informed our understanding of signal transmission at the neuromuscular junction (Furshpan and Potter, 1959), the role of glutamate and

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GABA as excitatory and inhibitory neurotransmitters (Molinoff and Kravitz, 1968; Otsuka, 1996; Tomiko et al., 1983), the neural orchestration of escape (Edwards et al., 1999), the detailed organization of pattern-generating networks (Nusbaum, 2001), and the role of modulatory neurochemistry in complex behaviors such as aggression (Kravitz, 2000). At the organismal level, moreover, variation in developmental process, growth, life span, reproduction, and stepwise phenotypic changes of metamorphosis, allow accurate longitudinal analysis of various behaviors during drug conditioning and states. The universal nature of these findings arises from the fact that all metazoan life shows exceedingly deep homologies in neural signaling (Pandey et al., 2013; Vernier, 1995; Vernier et al., 1997), neurochemical modulation (Blenau and Thamm, 2011; Tierney, 2001), paralogous receptor elements (Hen, 1992, 1993; Katz and Lillvis, 2014), and associations of neural mechanisms with similar behavioral contexts (Egnor and Branson, 2016; Kravitz, 2000). A companion paper discusses the presented work from physiological and pharmacological perspectives (Shipley et al., 2017). The present review explores the evolutionary, natural history, and behavioral implications of natural and drug-sensitive reward in crayfish, offering a wider perspective for addiction research across all metazoans.

Despite these clear advantages, simpler systems have been greatly underutilized in studies of more complex phenomena, such as cognition, affective states, or addiction. The likely reason may be that complex forms of learning, executive control, andnatural and drug-sensitive reward, are regarded as phenomena too rich, nuanced, and evolutionarily distant from the generally accepted capabilities of invertebrates. The dearth of comparative perspectives is particularly striking for research into the rewarding properties of addictive drugs, the vulnerabilities for compulsive drug seeking, and the neural and genetic determinants of behavioral dependence. Surely 'cockroaches with claws' can tell us little about addiction, a phenomenon widely considered to be uniquely mammalian, securely seated within the cognitive realm, and involving terms such as 'wanting', 'craving', and 'desiring'. The present paper aims to challenge this view using several lines of empirical evidence. Specifically, we demonstrate in crayfish the presence of many key behavioral features that are commonly used to validate addiction-like phenomena in other non-human primate/mammalian study systems. We summarize data on (1) unconditioned drug effects and changes in motivation, such as intoxication, psychostimulant sensitization, and compulsive drug-seeking and taking, (2) drug-elicited cue learning using conditioned preference paradigms, and (3) instrumental components of addictive processes via drug-sensitive reward and operant self-administration protocols.

Explanatory concepts for the implementation of mammalian drug addiction focus on a number of neuromodulatory axes, such as mesolimbic dopamine (Alcaro et al., 2011). All metazoans are thought to share biogenic monoamine neuromodulation, including axes centered on serotonin, dopamine, epinephrine, and others. Comprising a class of small, modulatory signaling molecules, amines are attractive candidates for complex behavioral modulation as they impact neural function at multiple levels and adjust the individual's behavior to external demands. Based on evidence from a wide range of invertebrate models, they selectively sensitize/depress sensory elements, organize neuronal activity in central circuits, bias motor systems towards contextually appropriate states (Menzel, 2012), and alter the activity of neural decision-making centers (Nader et al., 1997). Rather than producing behavior *per se*, these substances promote the occurrence of adaptive behaviors in specific contexts e.g. flight, fight, or mating (Kravitz, 1988; Heinrich et al., 2001). Unfortunately, these are the exact properties that also make neuromodulators so inherently difficult to study. The ability in crayfish to combine robust quantitative behavioral analyses with particulars of biochemistry, pharmacology, physiology, and molecular genetics (Lederhendler and Shulkin, 2000; Chen et al., 2002; van Staaden and Huber, 2001) offers a number of distinct advantages for the work described here.

As is the case with humans, it is clear that a wide range of mammals will work long and hard to obtain psychostimulant drugs through compulsive self-administration (Johanson et al., 1976; Wise, 1998). Such addictive properties likely involve the action of specific reward pathways. In response to selective pressures, the activation of natural reward systems usually aligns with an individual's adaptive goal, enticing it to satisfy inherent motivations for nourishment, sex, or 'contact comfort' (Panksepp et al., 2002). Dopamine projections from the ventral tegmental area to the nucleus accumbens, are integral elements underlying feelings of desire in humans and have been widely conserved throughout mammalian evolution. Moreover, compulsive aspects of addictive behaviors map onto motivational, subcortical neural circuits, with strong anatomical, neurochemical, and possibly motivational homologies shared across all mammals and even across other non-mammalian vertebrates (Butler and Hodos, 2005). Addictive compounds are thus likely to act on evolutionarily conserved brain substrates for reward beyond those unique to humans. During the addictive process then, natural reward systems are being commandeered by highly purified chemical compounds, which promote compulsive behavior, even as they result in negative outcomes such as starvation (Wise, 1998).

Several lines of thought have begun to soften the mammalian-centric perspective of drug addiction as a psychological predicament, amenable to cognitive solutions. Our societal predicament with drug addiction arises from the fact that a learned pairing between a set of environmental cues and a drug, stubbornly resists efforts to extinguish it through cognitive resolve and behavioral modification therapy. Exploring the role of consequences in addiction, Heyman recently concluded that addicted individuals display key hallmarks of free will as defined by the capacity to voluntarily cease drug use and regulate their cravings (Heyman, 2017). Drug-induced conditioning in humans, however, appears notoriously recalcitrant to treatment with cognitive approaches. Even after decades of drug-free condition and continued drug-treatment efforts, craving readily reinstates in former addicts. Relapse may be triggered by an encounter with drug paired cues, exposure to a small, priming dose of the drug, or stress (Koob and Volkow, 2016; Milivojevic and Sinha, 2018). The definition of the disease centers on the very fact that suffering individuals struggle to exert cognitive control over their behavior as they vigorously pursue and consume drugs even in the face of intensely harmful consequences. An alternative explanation for this paradox may arise in a different line of argumentation. Acting on neurochemical systems with features highly conserved across the entire metazoan radiation, the behavioral effects of addictive compounds might reside in more fundamental mechanisms than previously recognized. All natural compounds with stimulant and addictive properties, including nicotine, ephedrine, cocaine, cathinone, or morphine, are secondary plant metabolites (alkaloids), serving a role in plant defense against herbivory (Wink, 2015). Leaving aside for now the fact that production of defensive compounds with addictive potential appears counterintuitive (the topic is addressed in a later section of the paper), the principal targets of such a defense are most certainly arthropods, the dominant herbivores since the early evolution of land plants (Labandeira, 2007). 'Human drugs of abuse' may thus more aptly be recognized as 'Arthropod drugs of abuse', which extend their destructive consequences to primates because of the conserved biological roots of motivation, reward, and learning. Rather than viewing addiction as a uniquely mammalian phenomenon, causal understanding and effective therapies may be more productively sought via a view of addiction as a fundamentally arthropod phenomenon, with humans as collateral damage owing to the conserved nature of drug neural targets.

Addiction manifests in a variety of ways, including impaired response inhibition and increased salience attribution, altered perceptions of reward strength, and compulsive drug-seeking and consumption despite adverse consequences (Koob, 2015; Fattore and Diana, 2016). Our early work demonstrated that several human drugs of abuse yield robust psychostimulant and rewarding properties in crayfish