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Editorial

Addiction: A preclinical and clinical analysis

1. Introduction

This Mini-Issue of the Brain Research Bulletin emerged from the first annual Addiction Symposium held at the Pennsylvania State University College of Medicine on the 15th and 16th of January 2015. The goal was to bring together students, faculty, basic scientists, clinicians, physicians, state representatives, senators, and leaders of area treatment facilities to: (1) Discuss novel preclinical and clinical data as they contribute to a better understanding of the disease; (2) Learn about current challenges facing our Emergency Rooms, clinics, community, and state in the treatment of addiction; and (3) Discuss policy changes implemented through the Affordable Care Act (ACA) that require long-term treatment for this long-term chronic brain disease and provide for enhanced physician education. The latter conversation was led by our keynote speaker, Dr. A. Thomas McLellan, co-author of the ACA as it pertains to addiction. In this commentary (see Woodworth and McLellan, 2016), evidence is presented suggesting that a policy change stands to revolutionize prevention and treatment of Substance Use Disorder and addiction in the United States.

2. Addiction: the problem

It is estimated that about 15% of the population is vulnerable to the development of drug and alcohol addiction (Anthony et al., 1994). With regards to opioids and nicotine, estimates are even higher with about 50% of those exposed evidencing dependence (Hughes et al., 2006; SAMHSA 2012). The social and economic consequences are great. Addiction costs the United Stated an estimated $700 billion each year (National Institute on Drug Abuse, 2015); 480,000 people die each year from smoking related deaths (U.S. Department of Health and Human Services, 2014); 70% of those in state prison and 64% of those in federal prisons regularly used drugs prior to incarceration (National Institute on Drug Abuse, 2014); and death by overdose is currently the leading cause of injury-related death in the United States, having doubled over the past 14 years and now exceeding motor vehicle-related deaths in 36 states and Washington, DC (Levi et al., 2015).

3. Addiction: the need for translation

Given the severity of the problem, it is essential to bring together preclinical and clinical scientists in an effort to advance our understanding of this disease and to facilitate research on novel treatments. It is important that we understand the etiology of addiction. How does it start? When does it start? Who is vulnerable? Who is resilient? Why? What factors increase risk or resilience and how do they affect the brain for better or for worse? The present set of papers reflects a dialog between basic and clinical scientists involved in the study of addiction and our recent efforts to begin to address some of these critical questions. Of course, our findings, like all others, fall on deaf ears if science, even translational science, fails to impact policy. Thus, in the final paper, Woodworth and McLellan (2016) discuss how implementation of the Affordable Care Act will apply what science has taught us about best practices to the effective prevention and treatment of addiction.

4. Understanding addiction: the utility of animal models

The usefulness of clinical data is transparent. The usefulness of preclinical data, on the other hand, depends in large part upon the validity of the animal model employed. Not surprisingly, there is no shortage of animal models for the study of addiction. Model development has progressed to include models of sensitization (Puhl et al., 2015) and conditioned place preference (Rorabaugh et al., 2015). Self-administration of drugs of abuse has been studied for decades and schedules of reinforcement have been honed to include, among others, fixed ratio schedules for the measurement of the amount of drug self-administered, progressive ratio schedules to index how hard a rat is willing to work for drug (Oleson and Roberts 2009), and short (e.g., 1 h) vs. long access (e.g., 6 or more h of access to drug daily) to allow for an assessment of escalation of drug taking over time – a key feature of human substance use disorder and addiction (Koob and Kreek 2007; Wade et al., 2015). Another animal model holds drug self-administration constant (i.e., drug self-administration does not escalate), but reveals individual differences in seeking during periods of signaled non-availability of drug, the willingness to work for drug during progressive ratio testing, and the persistence of responding for drug in the face of adverse consequences (Deroche-Gamonet et al., 2004; Kasanetz et al., 2010). Yet, another animal model pits a sweet against a drug in a 2-choice test and reveals that sweets can be highly preferred over drug (Lenoir et al., 2007). Finally, a model that we employ uses brief access to a sweet cue (usually saccharin) to predict the future opportunity to self-administer a drug of abuse. Using this model, large individual differences are evident very early (within a matter of a few trials) and greater avoidance of the drug-paired cue is associated with greater drug seeking and taking (Colechio

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and Grigson 2014; Grigson and Twining 2002; Imperio and Grigson 2015; Twining et al., 2009). These findings are consistent with data suggesting that addiction is a learned phenomenon and indicates that this learning begins with the first exposure to drug. Collectively, there is a great deal of utility in all of these animal models and several have been employed in the papers that appear here. Each has its place, with the caveat that we must come to understand, as well as is possible, what a given paradigm is modeling, its strengths and, importantly, its limitations. These data, then, can be combined with clinical data to inform our understanding of the development of addiction, factors that influence its progression, and novel avenues for treatment.

5. Papers in this mini-Issue: risk factors for addiction

There are all manner of risk factors for addiction, many of which are beyond the scope of this Mini-Issue. One major risk factor, however, one over which we have no control, involves our genetic makeup. A case in point involves the A118G allele. Recent data have linked the inherited A118G allele with an increased risk of substance abuse and addiction in humans (Bart et al., 2005). Using mice, Henderson-Redmond et al. (2016) examine the role of the human A118G allele in response to the rewarding and the antinociceptive effects of morphine. Another risk factor relates to critical periods of development. Adolescence clearly is one of the critical periods during which exposure to drug can exert life-long changes in brain and behavior. Locker et al. (2016) show that nicotine exposure during adolescence impacts later ethanol intake in mice and the binding of nicotinic cholinergic receptors in brain. Of course, until recently, humans were rarely exposed to nicotine in the absence of numerous toxicants. With the introduction of e-cigarettes, however, this is no longer the case. E-cigarette sales more than doubled between 2012 and 2013 in the United States (Giovenco et al., 2014) and the number of never-smokers trying e-cigarettes is increasing, particularly among younger users (Carroll Chapman and Wu 2014; King et al., 2013). That being said, we know very little about what initiates and sustains the use of e-cigarettes and little is known about the impact of nicotine, administered via this novel delivery system, on the brain and on craving. For the first time, Nichols et al. (2016) examine the impact of exposure to electronic cigarette video cues on the urge to "vape," and, using fMRI, on the activity of the brain in human electronic cigarette users before and after use of the product.

Sleep deprivation poses another risk factor for addiction. Approximately 30% of people sleep at most 6 h per night (Schoenborn et al., 2013) and insufficient sleep contributes to initiation of drug abuse in teenagers (Mednick et al., 2010; Tynjala et al., 1997; Wong et al., 2004, 2009) and to later addiction (Gillin 1998). In a rodent model, acute sleep deprivation increases the rate at which rats self-administer cocaine (Puhl et al., 2009), and chronic sleep deprivation, on the order of that experienced by humans, facilitates acquisition of cocaine self-administration and increases the willingness to work for drug (Puhl et al., 2013). Although there are many reasons why humans might be sleep deprived, the act of drug-taking, itself, may be disruptive. To examine this possibility, Coffey et al. (2016) describe robust changes in sleep architecture in rats across the addiction cycle (i.e., during acquisition, abstinence, and reinstatement of heroin-taking and seeking behavior). One risk factor that recently became evident in the human population could not be anticipated. Specifically, humans undergoing Roux-en-Y gastric bypass (RYGB) surgery for obesity have an increased risk for substance use disorders (Dutta et al., 2006). The mechanism for this is unknown. Thus, in an effort to begin to explore this phenomenon, the Hajnal laboratory developed a rodent model to examine how RYGB surgery might augment responding for ethanol or drugs of abuse (Hajnal et al., 2012; Polston et al., 2013; Thanos et al., 2012). Using this model, Biegler et al. (2016) demonstrate the impact of gastric bypass surgery on acquisition of morphine self-administration in rats. Finally, having explored a number of risk factors, one paper seeks to intervene. Venkiteswaran et al. (2016) test whether transplant of L-Dopa secreting retinal pigmented epithelial cells into the shell of the nucleus accumbens will rescue vulnerable rats from seeking cocaine following a period of abstinence.

6. Addiction and devaluation of natural rewards

Addiction would be of much less concern were it the case that the addict continued to actively engage in normal daily life. This, however, is not the case. The addict pays less attention to his or her health (Santolaria-Fernandez et al., 1995), is more likely to be absent from work (Jones et al., 1995), and more likely to have his or her children removed from the home due to neglect (Nair et al., 1997). The final set of research papers address drug-induced devaluation of natural rewards in a rodent model and in recovering human opioid addicts. In an effort to better understand how one model of addiction interfaces with another, Jenney et al. (2016) test whether large suppressors of the heroin-paired saccharin cue following just 3 taste-drug pairings will evidence high 'addiction-like' behavior when tested with intermittent drug access in a variation of the model used by Deroche-Gamonet et al. (2004). Jenney's study goes on to link these differences in behavior to differences in the expression of mu opioid receptor interacting proteins (MORIPs) and a D2 receptor interactor in the prefrontal cortex, nucleus accumbens, hippocampus, and ventral tegmental area. Imperio and Grigson were the first to combine avoidance of the drug-paired cue with extended access to heroin (Imperio and Grigson 2015). In so doing, they reported that greater avoidance of the heroin-paired saccharin cue was accompanied by not only greater drug-seeking and taking, but also by greater escalation of drug-taking over time. Here, Imperio et al. (2016) link these individual differences in behavior to individual differences in the expression profile of a range of genes in the nucleus accumbens via next generation gene sequencing. McFalls et al. (2016) examine how such individual differences in avoidance of the heroin-paired saccharin cue are associated with individual differences in the expression of genes in the corticotrophin releasing hormone (CRH) signaling pathway in the prefrontal cortex, hippocampus, ventral tegmental area, and nucleus accumbens. Interestingly, these preclinical findings are paralleled by clinical work where Huhn et al. (2016b) use functional Near Infrared Imaging (fNIR) to track the behavioral and neural (prefrontal) response to natural rewards and ecological momentary assessment (Huhn et al. 2016a) to track affect and craving in recovering opioid addicted humans.

7. Addiction: a change in education and policy

While we have learned a great deal over the last several decades regarding the impact of drugs on brain and behavior, this new knowledge has yet to impact how the public (and insurers) views an individual with a substance use disorder, how a physician deals with such a person, or how addiction is treated in the clinic. As described by Woodworth and McLellan (2016), addicted individuals still suffer from remarkable stigma, isolating them in their illness and decreasing the likelihood that they will seek treatment. When help is sought, the person often faces an uncomfortable physician who is not trained to address addiction much less to provide real and lasting treatment. This failure is due, in part, to a failure to adequately teach the disease of addiction to hospital staff, medical students, residents, and physicians. Published data show that