Brain Research Bulletin xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Editorial

Addiction: A multi-determined chronic disease

This Brain Research Bulletin Special Issue on Addiction emerged from the Third Annual Addiction Dinner and Symposium held at the Pennsylvania State University College of Medicine on the 3rd and 4th of April 2017. The goal of this annual event is 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 allow for a better understanding of the disease of addiction; (2) Learn about current challenges facing our emergency rooms, clinics, community, and state in the treatment of substance use disorder (SUD) and addiction; and (3) Consider novel avenues for improved diagnosis and treatment of this chronic brain disease. The Keynote Speaker at the Addiction Symposium was Dr. Wilson Compton, Deputy Director for the National Institute on Drug Abuse (NIDA), who provided an overview of the problem of addiction at the national level and insight into cutting-edge research and the development of novel therapeutic interventions. The Keynote Speaker at the Addiction Dinner was Dr. Robert L. DuPont, former Director of the National Institute on Drug Abuse, first Drug Czar, and current President of the Institute for Behavior and Health. In his commentary (DuPont, 2017), the final paper in this series, Dr. DuPont addresses the state of the opiate epidemic, and the need for prevention and long-term treatment of this devastating chronic disease of the brain and behavior.

1. Addiction: the problem

It is estimated that, with use, and depending upon the drug, about 8–23% of the population is vulnerable to the development of drug and alcohol dependence (Anthony et al., 1994; Wagner and Anthony, 2002). With that, addiction costs the United Stated an estimated $400–740 billion each year (U.S. Department of Health and Human Services (HHS) Office of the Surgeon General, 2016; National Institute on Drug Abuse, 2017a, 2017b); 480,000 people die each year from smoking related deaths (U.S. Department of Health and Human Services, 2014); 88,000 people die each year from alcohol related causes (Mokdad et al., 2004); drugs and alcohol are involved in more than 75% of violent and property crimes (The National Center on Addiction and Substance Abuse at Columbia University, 2010); the incidence of neonatal abstinence syndrome increased 5 fold from 2000 to 2012 (Patrick et al., 2015); and death by drug overdose is a recognized national epidemic, exceeding the number of deaths due to motor vehicle-related accidents (Warner et al., 2011; Stewart, 2016). In 2016, drug overdose deaths numbered at least 59,000, a near 20% jump from the number recorded in 2015, and the largest annual increase on record (Katz, 2017). That being said, there is some reason for hope. First, with new preclinical and clinical research, we continue to better understand underlying mechanisms of the disease and factors that contribute to the development of SUD and addiction. In so doing, we begin to uncover novel avenues for diagnosis and treatment. Such in vitro and in vivo (animal and human) research will be addressed in this issue involving the study of nicotine, ethanol, cocaine, and opiates. Second, according to DuPont (2017), life-time abstinence from nicotine, marijuana, and alcohol in 12th graders in 2014 was 5 fold greater than that reported in 1983. Finally, with *appropriate long-term treatment*, sustained abstinence shifts from an unlikely occurrence, to a probable outcome (see (DuPont, 2017) in this issue for a discussion;(Hall et al., 2009)).

2. In this issue: ethanol

The data described in the papers in this issue make it clear that the development of SUD and addiction is affected by a range of factors including age, sex, genes, experience, and drug. In the manuscript by Aimino et al. (2017), we learn that the neural mechanisms mediating the effects of ethanol are complex, even at the level of the nucleus of the solitary tract in the medulla, and that multiple “cell-type” and “synapse-specific” effects may work together to impact the development of alcoholism. Genes, too, impact the expression of disease. Henderson-Redmond et al. (2017) show that ‘humanized’ mice expressing the mu opioid receptor A118G single nucleotide polymorphism (118GG) drink more alcohol than their 118AA counterparts. The impact of this allele on ethanol intake is similar between male and female mice, though female 118GG mice show the least ataxia, and male 118GG mice show greater ethanol conditioned place preference than their respective 118AA controls. These data are taken as evidence that, as with humans (Bart et al., 2005), the A118G allele confers vulnerability to addiction, but that ethanol drinking may be driven by different sensitivities in males and females. Developmental stage is another well known factor in the onset of alcohol use disorder (AUD) and addiction. Here, Kamens et al. (2017) show that, unlike findings in adult mice (Kamens et al., 2010a, 2010b), treatment with the nicotinic acetylcholine receptor partial agonist, varenicline, reduces ethanol and sucrose intake in adolescent male and female mice, without affecting ethanol-induced ataxia or sedation. Vulnerability to the effects of alcohol, then, is impacted not only by genetic background, but also by sex and stage of development, and each can engage different systems and different underlying neural mechanisms. Finally, novel factors contributing to AUD also have been revealed via a circuitous route. Specifically, it has been discovered that while Roux-en-Y gastric bypass (RYGB) surgery greatly reduces obesity, it also leads to

https://doi.org/10.1016/j.brainresbull.2017.11.019

an increase in new cases of AUD in this patient population (King et al., 2017). An alternative surgical approach, the vertical sleeve gastrectomy (VSG), is nearly as effective in reducing body weight, but is reported to have less of an impact on the development of AUD (King et al., 2012; Suzuki et al., 2012; Conason et al., 2013; King et al., 2017). Here, Orellana et al. (2017) develop the first animal model to study this finding and show that VSG reduces body weight in obese rats, while decreasing, rather than increasing, ethanol intake. Importantly, via this sophisticated animal model, a key role for ghrelin signaling also is revealed.

3. In this issue: nicotine

In 2015, 10.5% of 12th graders surveyed smoked cigarettes over the past month, as did about 20% of those ages 26 or older (National Institute on Drug Abuse, 2017a, 2017b). Ultimately, as stated, smoking is linked to 480,000 deaths annually (Centers for Disease Control and Prevention, 2016). As with other addictions, the transition from initial nicotine use to substance use disorder and addiction is impacted by a number of factors including age, sex, genes, and experience. Of the relevant experiences, stress is one that goes hand-in-hand with nicotine use. Indeed, as described in this issue, stress impacts an individual's response to nicotine and nicotine impacts an individual's response to stress. Thus, Caruso et al. (2017) show that adolescent exposure to chronic variable social stress leads to an increase in nicotine-induced locomotion during late adolescence. During adulthood, male mice exposed to adolescent stress exhibited an increase in nicotine-induced corticosterone secretion and a decrease in voluntary nicotine intake. Finally, adolescent stress resulted in a persistent reduction in exploratory locomotion when male mice were exposed to novel environments. The effects are largely absent in adolescent and adult females. In turn, Kutlu et al. (2017) demonstrate that nicotine exposure slows extinction of a fear memory and increases spontaneous recovery of that memory in adult mice, but not in adolescents. These data have important implications for adults with post-traumatic stress disorder (PTSD) and the potentially facilitative effect of nicotine exposure on fear memories. Finally, e-cigarette use is on the rise, with 12.5% of 12th graders having smoked e-cigarettes within the past month (National Institute on Drug Abuse, 2017a, 2017b). While e-cigarettes also contain nicotine, e-cigarettes often are viewed as a safer alternative to combustible cigarettes because the level of toxicants is 9–450 times lower (Goniewicz et al., 2014). Even so, relatively little is known about the impact of e-cigarettes on brain, particularly on reward circuitry. Hobkirk et al. (2017) used fMRI to begin to address this gap in knowledge and show in this issue that acute e-cigarette exposure induces patterns of brain activity like those elicited by combustible cigarettes, i.e., patterns of activity linked to craving and withdrawal. Thus, while e-cigarettes expose the smoker to fewer harmful chemicals, the imaging data suggest that e-cigarettes too are potentially addictive − as indicated by the activation pattern in brain. Clearly we need to protect young people from all forms of nicotine dependence and to develop a better understanding of the relative harmfulness and addictiveness of e-cigarettes versus smoked tobacco (Leventhal et al., 2015; U.S. Department of Health and Human Services, 2016).

4. In this issue: opiates and opioids

For better or worse, opiates (e.g., morphine) and opioids (e.g., oxycontin) are the first line of defense against pain. Indeed, not long ago, pain was promoted as the 5th vital sign and physicians were discouraged from leaving pain untreated. The result was a remarkable increase in the writing of prescriptions for opioid pain medications which were, initially, billed as non-addictive. The incidence of opioid use disorder and addiction has since skyrocketed, and with it, as discussed, the number of overdose deaths. To date, 600,000 deaths are estimated to have occurred due to opioid overdose in the United States alone, and 180,000 more deaths are expected by 2020 (Blau, 2017). These are devastating numbers. Importantly, while many of these deaths are found to involve heroin or, more recently, fentanyl, 80% of all new heroin users have experience with prescription opioids (Gostin et al., 2017). The taking of one, then, often leads to the taking of the other.

The effective and safe use of opioids for the treatment of pain, however, is complicated and, like other abused substances, varies as a function of the factors described above (e.g., sex, age, genes, experience, etc). An additional factor that impacts the effectiveness of opiates for the treatment of pain is diet. Here, Nealon et al. (2017) show that male and female mice fed a high energy diet (high fat/high sucrose) exhibited greater tolerance (i.e., less responsiveness) to the antinociceptive effects of morphine in both the tail flick assay and in the formalin inflammatory pain model. These findings are consistent with some reports showing increased sensitivity to pain in obese humans (Stone and Broderick, 2012) and a need for greater opiate/opioid treatment in this patient population (D'Arcy, 2015). Diet and obesity, then, are additional factors to take into account when considering the use of opiates or opioids for the treatment of pain.

In humans, continued use of drug, SUD and addiction involves devaluation of natural rewards (Jones et al., 1995; Santolaria-Fernandez et al., 1995; Nair et al., 1997; American Psychiatric Association, 2000; Goldstein et al., 2007) and vulnerability to relapse even following extended periods of abstinence (Yang et al., 2008). This has been modeled in rats and mice who avoid intake of an otherwise palatable sweet cue (usually saccharin) when it predicts the availability of a drug of abuse (Grigson, 1997; Twining et al., 2016). In this case, avoidance is thought to be mediated by devaluation of the sweet in anticipation of the pending availability of drug and the onset of an aversive state of conditioned craving and withdrawal (Grigson, 2008). Importantly, greater avoidance of the drug-paired saccharin cue is associated with a shorter latency to take drug and greater seeking and taking (Grigson and Twining, 2002; Imperio and Grigson, 2015). That being said, the comparative relationship between the sweet and the drug is bi-directional: The drug can devalue the sweet; and the sweet can devalue the drug. In accordance, Freet and colleagues have shown that some sweet-preferring strains of mice exhibit less avoidance of the drug-paired sweet cue than their less sweet-preferring counterparts (Freet et al., 2009; Freet et al., 2013). Here, in this issue, Freet et al. (2017) show that 'humanized' mice containing the variant 118GG allele also exhibit less avoidance of a heroin-paired saccharin cue than do mice containing the wild-type 118AA allele. This effect, however, appears to be drug dependent, as it occurs when saccharin predicts experimenter delivered heroin, but not cocaine (Freet et al., 2015). Jenney et al. ((2017) this issue) also compare avoidance of a saccharin cue when paired with experimenter-delivered morphine or cocaine in male and female Sprague-Dawley rats. The results, again, reveal drug dependent effects whereby female Sprague-Dawley rats exhibit less avoidance of the cocaine-paired, but not the morphine-paired, saccharin cue than their male counterparts. In each case, these data must be taken, at the very least, as a cautionary note not to generalize, carte blanche, the findings from one drug to another. Regardless, responsiveness to the taste cue in this paradigm can be highly informative. In this issue, Colechio et al. (2017) show that, while addiction often is thought to develop gradually over time, the most vulnerable individuals evidence the onset of the addiction process upon the first exposure to drug and early onset of this addiction process predicts greater escalation of later cocaine self-administration behavior. In this case, a similar pattern is evidenced with avoidance of a heroin-paired saccharin cue (Imperio and Grigson, 2015). Future efforts should seek a human corollary in an effort to identify, a priori, vulnerable individuals.

Whether an individual is identified as vulnerable to onset of the disease or already in the throes of addiction, intervention is needed. Here, despite many promising findings, we continue to come up short − at least with respect to a pharmacological intervention. As such, it is critical that novel