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Animal models of addiction: Compulsive drug taking and cognition

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Substance use disorders (SUDs) are biopsychosocial states that consist of neuropsychiatric symptoms including loss of control of drug taking, continued drug use in the presence of adverse consequences, and repeated relapses to drug taking after intervals of forced or voluntary abstinence. SUDs are accompanied by cognitive deficits that also vary according to abused substances (Cadet and Bisagno, 2016). The importance of cognition and SUDs is very well covered by Sampedro-Piquero et al. and Table 1 in their review provides a comprehensive summary of papers supporting the existence of cognitive deficits in patients who used amphetamine, cocaine, marijuana, and opioid drugs. Cognitive deficits are thought to be secondary to a diversity of neuropathological changes reported in varied addicted human populations (Cadet et al., 2014). It is important to note that neuropathological substrates can be distinct even when cognitive manifestations are similar in various neurological patient populations.

Sampedro-Piquero et al. have included an excellent section on beneficial effects of environmental enrichment (EE). Those observations were made in animal models of addiction including drug self-administration. It is, important, to point out that therapeutic use of EE in animal models may not expound the breadth necessary to generate comprehensive cognitive theories of human SUDs. More relevant to the subject of the paper is the review of clinical application of cognitive therapeutic approaches. This was very well done. Indeed, the care of humans who suffer from SUDs needs more comprehensive approaches that include cognitive therapies and the development of pharmacological agents that enhance cognitive functions. I submit further that these approaches will be much more beneficial to our patients than attempts to use medications that had suppressed drug-taking behaviors in rodents.

It is therefore relevant to this discussion that we take a more analytical stab at the preclinical models used to inform neurobiological theories of addiction in humans. The special issue contains several excellent reviews of animal models. Of significant interest in the review by Lamontagne and Olmstead who discuss a dimensional approach to animal models that might be more representative of symptom clusters observed in humans. This is an important issue because investigations of escalation of drug intake by rodents during drug self-administration experiments have been the main approach to addiction research in animals. Indeed, escalation of drug intake by animals in those settings is thought to be tantamount to

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addiction in humans (Ahmed and Koob, 1998). Experimentally, rodents are usually given daily access to drugs for 6–12 h. Animals, given long access to drugs, do escalate their drug intake over variable time intervals depending on the experimental substance under study. Nevertheless, the conclusion that escalation of drug intake is equivalent to addiction is not tenable when human data are considered because only a relative minority of individuals who had escalated their drug use during high school or college subsequently meet diagnostic criteria for SUDs according to the Diagnostic Statistical Manual of the American Psychiatric Association. Moreover, the diagnosis of SUDs is based on meeting various criteria, with drug taking behaviors being only one of these criteria. It is, thus, erroneous to state that there exists a one-to-one correspondence between escalation of drug use in rodents and clinical diagnosis of addiction in humans. It is also fallacious to suggest that these rat models represent the totality of clinical conditions of humans who become and remain addicted in the presence of varied adverse psychosocial consequences. Those addicted patients are the ones whose cognitive functions are detailed in the review by Sampedro-Piquero et al. It is really a pity that not enough research has been conducted in populations who abuse drugs but never meet criteria for SUDs because these types of investigations would help to identify cognitive effects of drug exposure in the absence of addiction. Another issue that needs to be addressed in longitudinal studies is whether or not cognitive deficits might have preceded a SUD diagnosis.

To better mimic a DSM criterion of addiction, some investigators have introduced adverse consequences in self-administration studies. Those experiments were not covered in the special issue and are worth mentioned for the sake of thoroughness. In these studies, most rats, given long access to drugs escalate their drug intake during self-administration training. However, a majority of these rats suppress (punishment-sensitive) their intake of cocaine or methamphetamine when footshocks are contingently applied during subsequent phases of the experiments (Cadet et al., 2019). A smaller group of rodents continues to compulsively self-administer drugs (punishment-resistant). Resistant and sensitive phenotypes are thought to represent individuals who meet or do not meet DSM criteria for SUDs, respectively (Cadet et al., 2019). Of relevance to the Sampedro-Piquero review, Chen et al. (2013) had reported substantial decreases in intrinsic excitability in neurons located in the prelimbic cortex of punishment-resistant rodents that self-administered cocaine. They showed further that optogenetic stimulation of the prelimbic cortex, an area of the brain known for its involvement in cognitive functions, could decrease compulsive drug-seeking in the resistant animals. These results suggest that therapeutic approaches that involve stimulation of pathologically affected brain regions in addicted humans need further investigation. This line of reasoning is consistent with the data reviewed by the groups of Luquiens et al. and Sampedro-Piquero et al.

In summary, this special issue on addiction provides the initiated and novice with excellent reviews of animal models of addiction and of potential cognitive consequences of SUDs. In this commentary, I have discussed some issues that need to be considered when reading preclinical studies offered as addiction models. The introduction of adverse consequences in self-administration studies supports the dimensional approach discussed by Lamontagne and Olmstead in this issue. It will therefore be important to use preclinical investigations to identify potential cognitive deficits in divergent rat phenotypes that represent addicted and

nonaddicted animals. These studies should help to elucidate the functional neurobiology of cognitive deficits in SUD populations.

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