“Mourning” a lost opportunity

Peter W. Kalivas · Cassandra D Gipson

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The general theory proposed by Piazza and Deroche-Gamonet is a well-written compilation of largely behavioral literature relevant to the development of drug addiction. In synergy with many reviews over the last decade, they describe addiction as a spectrum disorder and propose three distinct steps of increasing compulsive use, each with its own underpinning neuropathology. They also remind us that drug addiction is a neurobiological disease and that, like all neuropsychiatric disorders, contains both genetic and epigenetic vulnerabilities. On top of these well-trodden concepts, the authors provide an interesting perspective derived from iterating between the clinical symptomatic description of drug addiction and animal models of drug use developed by themselves and others designed to mimic clinical symptoms. The first stage of addiction, referred to as recreational and sporadic use (ReS), is firmly based in modern thinking about how drugs of abuse promote dopamine transmission to reinforce behavior and facilitate learned associations. It is proposed that the large majority of people and animals are vulnerable to ReS, and this stage is nicely modeled in animals using standard self-administration protocols. Intensification of use (ISuE) is modeled by escalated drug intake in animals, and it is proposed that not all people or animals are susceptible to entering ISuE. The neurobiology of this stage is suggested to involve adaptations in dopamine and glucocorticoids, although the authors briefly acknowledge recruitment of a broader circuit substrate. Finally, full addiction is characterized by loss of control (LoC) that they suggest relatively few people or animals are vulnerable to developing, and is mediated partly by a loss of excitatory synaptic plasticity, as measured by a loss of long-term depression (LTD).

The three distinct stages that the review carves out of the addiction spectrum are derived in large part from the important contributions the authors have made over the last 20 years towards developing rodent models that capture anthropomorphic (face validity) aspects of the transition to addiction, in particular the ISuE and LoC stages. Unfortunately, in appropriately iterating between human addiction and the animal models, from our perspective, the review does a disservice by characterizing rat behavior with terminology that describes human states of motivation such as mourning, need, pleasure, and desire. This semantic iteration between animal models and humans seems an unnecessary segue in applying these elegant models to understand the neurobiology of addiction. True to the author's primary tenant that addiction is a neuropathology, it is the neurobiology, not the terminology that is most appropriately iterated between animal models of addiction and human disease. In the process of anthropomorphizing animal models, the review risks losing track of the two primary rationales for developing animal models of disease: (1) The model can provide an efficient screening mechanism for bringing new compounds or other interventions towards treating addiction in humans, or (2) The model can elucidate neurobiological changes that may be pathogenic in addiction, thereby providing a rationale for examining specific circuits or biomarkers in humans. Given the formative nature of our understanding of brain physiology and pathophysiology in general, we can add that a third general purpose of animal models is to understand how the brain works regardless of specific disease relevance.

Although the basic concept of impaired synaptic plasticity (LTD) was discovered using simpler, more efficient animal models of addiction (Martin et al. 2006), the review has appropriately highlighted the authors discovery of an enduring loss of LTD selectively in animals that show anthropomorphic signs of addiction (i.e., LoC stage). Thus, the authors provide us an example of the critical need to employ animal models in

P. W. Kalivas (✉) · C. D. Gipson
Medical University of South Carolina, Columbia, SC, USA
e-mail: kalivasp@muscc.edu

the discovery of neurological changes induced by the combination of drug use and genetic/epigenetic vulnerabilities that might contribute to human addiction. While the technology does not yet exist to determine if the LTD phenotype translates to human addicts, this preclinical work provides the biological rationale to advance clinical technologies, such as combining transcranial magnetic stimulation of frontal cortex with functional MRI measures in the nucleus accumbens to develop measures of LTD-like physiology as a biomarker of addiction. To our thinking, this type of neurobiological iteration with human addiction is a more useful vision for animal modeling of neuropsychiatric disease than the face validity of the model itself.

Along these lines, the review manifests one of the dangers in overemphasizing face validity relative to neurobiology, which is to shy away from the fact that regardless of anthropomorphic interpretations of rodent behavior, a lack of full correspondence between models and human disease is to be expected in distinct species with different environmental conditions for drug use. For example, the ISuE stage is modeled using extended access to drug and is characterized by escalating drug intake and motivation to obtain drug (Ahmed et al. 2002). Although a general interpretation of escalated drug use in long access paradigms is that it models the ISuE-like increased use of drug, recent evidence suggests that escalation is discriminative stimulus-dependent regulated intake (Beckmann et al. 2012). Within the same animal, both dysregulated and regulated intake can be demonstrated if session length is cued. Additionally, escalated intake can be seen within the temporal confines of regulated intake, indicating that when switching from shorter to longer access sessions, escalation can be a form of intake acquisition as animals learn a new temporal discrimination. These data indicate that escalation of drug use results, in part, from adaptive cortical and

allocortical learning processes and suggest that the neurobiology of escalated drug use may only partly overlap with the proposed human condition in the ISuE stage. Importantly, appropriately acknowledging a lack of behavioral/symptomatic correspondence with human addiction does not detract from the possibility that the model may still harbor neurobiological changes relevant to developing clinical treatments or biomarkers.

In summary, the authors have developed elegant rodent drug treatment protocols to support a proposal for how vulnerable subpopulations may transition to compulsive drug use and addiction. However, we wish the overall review would have more closely adhered to the philosophy embodied in its closing words, “science [in this case animal models] is certainly much better served from evolving what it is than from a durable what it should be”. Thus, the true value of animal models lies not in expanding anthropomorphic jargon and assuming functional causality by behaviorally reiterating what appear to be human traits, but in the model’s utility for discovering neurobiological mechanisms that may be relevant to understanding and curing addiction.

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