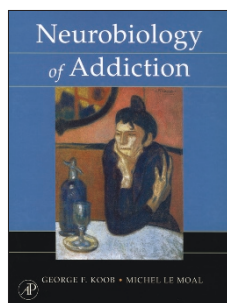


A walk on the dark side: addiction as allostasis



Neurobiology of Addiction

By George F Koob and Michel Le Moal

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Reviewed by Trevor W Robbins

Addiction neurobiology has seen astonishing advances in the last three decades. We now know the primary sites of action of virtually all drugs of abuse and are learning rapidly about molecular adaptations to chronic drug treatment. In an impressive and weighty new work, Koob and LeMoal assimilate several thousand references to provide a state-of-the-science proclamation of this progress, while setting our sights for its crucial next phases.

They achieve a balanced and well-informed commentary about their (strongly championed) positions on controversial areas in relation to competing views. They thus downplay the ‘incentive sensitization’ of the mesolimbic dopamine system as a crucial link in all forms of drug dependence. This view sees addiction as a cumulative process by which responsiveness to environmental stimuli associated with drugs is progressively enhanced through repeated use to produce aberrant activation of a basic appetitive system, equated with subjective ‘drug wanting’. Koob and LeMoal emphasize instead the importance of ‘opponent’ motivational processes, conceptualizing addiction as behavior directed toward escaping from progressively more aversive effects of drug withdrawal. A key insight is to think of these negative responses not only as physical symptoms, but also as psychological symptoms such as dysphoria—modeled in rats by the elevation in threshold for rewarding effects of brain stimulation. Koob and LeMoal also identify neurochemical and neuroendocrine sequelae of the opponent process, mediated by neural systems including the ‘extended amygdala’.

The regulation of stress is a prominent aspect of their theorizing, but they use the concept of ‘allostasis’ to capture the downward spiral of chronic drug abuse. Unlike homeostatic regulation about a fixed set-point, allostatic regulation allows the set point to fluctuate in response to the anticipation of future demands and life experience, even though this fluctuation is potentially pathological. Koob and LeMoal argue that the out-of-control aspects of drug addiction result from the allostatic pursuit—often in vain—of a fluctuating hedonic setpoint.

Trevor Robbins is in the Department of Experimental Psychology and at the Behavioural and Clinical Neuroscience Institute, University of Cambridge, Downing Street, Cambridge CB2 2EB, UK.
e-mail: twr2@cam.ac.uk

A central goal for future research must be to identify the causes of the transition to drug dependence or addiction. Koob and LeMoal emphasize that addiction is not simply drug self-administration *per se*. As a careful reading of the clinical criteria suggests, it is the narrow motivational (or compulsive) focus in some individuals that signals the transition to addiction. The factors underlying vulnerability to drug addiction are likely to be different from those simply promoting drug-taking behavior. The authors support the concept that early life stress is a major factor (together with predisposing genes), as with many neuropsychiatric conditions, but it is not clear how such a broad concept can explain the subtle interactions at each stage along the road to addiction (as well as the extensive comorbidities with other psychiatric disorders). The finding that rats will sometimes self-administer corticosterone itself indicates a need to move away from a simple, subjective concept of drug reward. Rather, such phenomena suggest attempts to attain a hypothetical optimum in brain activity through self-medication. In general, the field still has not sufficiently grappled with the fundamental issue, beyond basic pharmacological factors, of what it is precisely that makes a drug a reinforcer (that is, increases the likelihood of behavior upon which it is contingent).

A significant strength of *Neurobiology of Addiction* is the authors’ deep knowledge about the major classes of addictive drugs, including alcohol and nicotine, as well as the illicit cannabinoids, opiates and psychomotor stimulants. Five central chapters provide structured accounts of these main drug classes, including their often fascinating histories, medical effects and pharmacokinetics, as well as their basic behavioral pharmacology and abuse potential. The authors might have included more on treatments, past, present and future; I could not find “addiction treatment” or “medication” in the index, although relevant studies are described clearly in the text. However, this section, together with the excellent and informative opening chapters on definitions of addiction and animal models (arguably the best-developed and validated in behavioral neuroscience), enhance the value of the book as a reference or textbook for advanced students, as well as a scholarly synthesis. This value is augmented by the book’s attractive format, informative illustrations and case study appendices.

The penultimate chapter generously surveys contemporary hypotheses of drug addiction. I was struck by commonalities extending across the various theories that sometimes go unrecognized, being obscured by different terminologies. Koob and LeMoal could perhaps have done even more here to analyze the similarities and distinctive differences between the various positions. They do not always make it absolutely clear how certain lines of research they describe, such as distinct anatomical and functional components of the nucleus accumbens, relate to their own theoretical position. However, there is no mistaking the line taken in the concluding chapter in a ‘head-to-head’ confrontation of the allostatic and incentive sensitization views: they point out that addicts should take progressively less drug according to the incentive sensitization view and claim that “in animal studies, the literature linking increased self-administration to the sensitization process is not overwhelming.” Doubtless, this controversy will run and run.

The *Neurobiology of Addiction* is a thought-provoking *tour de force*. I expect it to become an instant classic and for future editions to gauge our progress in this exciting and compelling field. ■