Review

Biological Psychiatry

How Preclinical Models Evolved to Resemble the Diagnostic Criteria of Drug Addiction

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ABSTRACT

Drug addiction is a complex neuropsychiatric disorder that affects a subset of the individuals who take drugs. It is characterized by maladaptive drug-seeking habits that are maintained despite adverse consequences and intense drug craving. The pathophysiology and etiology of addiction is only partially understood despite extensive research because of the gap between current preclinical models of addiction and the clinical criteria of the disorder. This review presents a brief overview, based on selected methodologies, of how behavioral models have evolved over the last 50 years to the development of recent preclinical models of addiction that more closely mimic diagnostic criteria of addiction. It is hoped that these new models will increase our understanding of the complex neurobiological mechanisms whereby some individuals switch from controlled drug use to compulsive drug-seeking habits and relapse to these maladaptive habits. Additionally, by paving the way to bridge the gap that exists between biobehavioral research on addiction and the human situation, these models may provide new perspectives for the development of novel and effective therapeutic strategies for drug addiction.

Keywords: Behavioral models, Cocaine, Compulsive drug seeking, Limbic system, Substance use disorders

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Drug addiction is a complex neuropsychiatric disorder that affects a subset of the individuals who use drugs (1,2). It is defined as a compulsive relapsing disorder characterized by maladaptive drug-seeking habits maintained despite adverse consequences (3,4). The diagnosis of drug addiction has progressively evolved from pharmacology-related features, such as tolerance and withdrawal (in earlier versions of the DSM) to more psychological and behavioral features reflecting the compulsive nature of the disorder—maintained drug use despite adverse consequences in DSM-IV and the addition of drug craving in DSM-5 (5).

The modern study of the neuropsychopharmacologic mechanisms of drug addiction began with the development of the rat intravenous drug self-administration (SA) procedure in 1962 (6). This procedure is still the gold standard in the field, but as recognized years ago, allowing rats to lever press for intravenous or oral delivery of addictive drugs for several hours per day for a couple of weeks falls short of modeling human addiction (7). Additionally, despite the development in the 1970s (8,9) of reinforcement schedules that more closely mimic the complex drug-seeking behavior in humans, most studies use low rate fixed ratio (FR) reinforcement schedules to study mechanisms of drug reward (10–12), reinstatement after extinction (13–15), and relapse after forced abstinence periods (16–18) (Figure 1). The FR schedules in which animals receive a drug infusion on completion of the first ratio do not allow the investigation of the neurobiological substrates of drug-seeking behavior over protracted periods of time, a key psychological characteristic of individuals addicted to drugs (5).

New preclinical models of addiction (19–27) with better heuristic value with regard to the clinical definition of addiction have emerged. These models are based on SA procedures that have been refined to operationalize the core psychological constructs of the disorder—escalated drug intake (28,29), maintained drug use despite adverse consequences (21,22), and compulsive (24,26) drug-seeking habits controlled by drug-associated stimuli in the environment (30) that facilitate relapse after voluntary self-abstinence (23,27,31).

By focusing on late, but not early, stages of the addiction cycle (Figure 1), new preclinical models of addiction may help identify the neuropharmacologic and molecular mechanisms underlying the "addiction-vulnerable individual," filling the gap between clinical and preclinical research that has resulted in a failure to develop new effective treatments for addiction. In this review, we provide an overview of how preclinical models have evolved from Pavlovian and instrumental mechanisms of drug reinforcement to more recent models of addiction (20,32–34). We discuss the psychological processes from which each model stems, defining their interest and limits.

INSTRUMENTAL AND PAVLOVIAN MECHANISMS SUBSERVING DRUG USE: DRUG REINFORCEMENT

Drug addicts initially take drugs because they exert powerful effects on primary and secondary (i.e., conditioned) reinforcement mechanisms (35–38). The acquisition of SA of a drug is a behavioral marker of its reinforcing properties. The SA procedures can be arranged according to different schedules of reinforcement (39); the most commonly used schedule

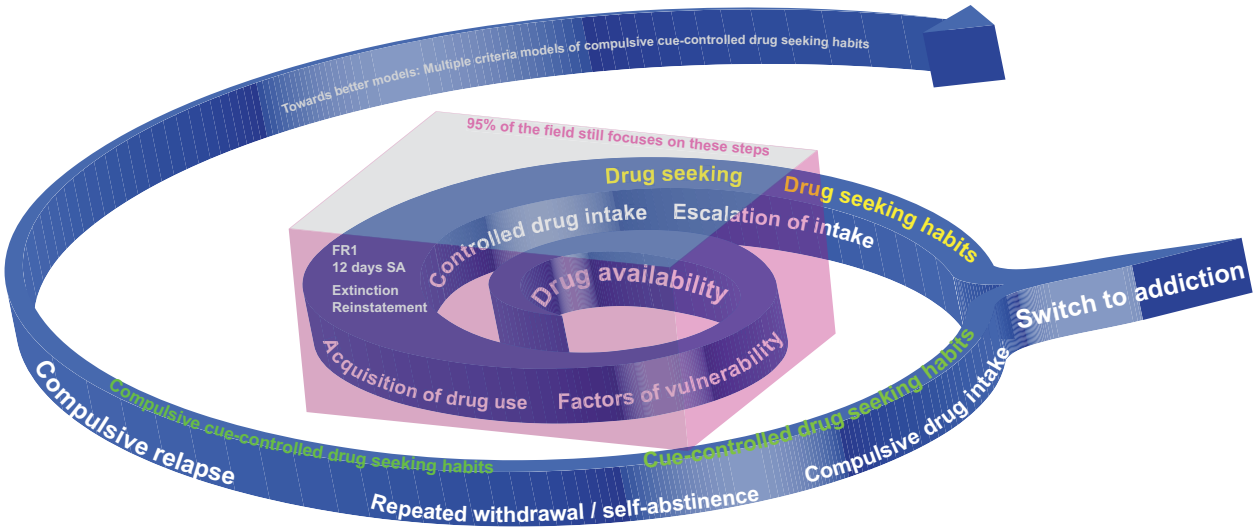

Figure 1. The drug addiction spiral and the various ways it is investigated in preclinical research. FR1, fixed ratio 1; SA, self-administration.

(Figure 1) consists of 10–12 daily 2-hour sessions of training under FR1 schedule (40–44), such that each lever press results in a drug infusion, often predicted by a contingent presentation of a discrete stimulus that becomes a conditioned stimulus (CS) through Pavlovian conditioning.

In FR schedules, the drug is delivered after the completion of a fixed number of responses by the animal, providing a direct relationship between the actual response and drug delivery so that the response rate of the animal, which remains stable over time, is determined by the unit concentration of the drug. In its classic form (FR, <2 weeks of training) (Figure 1), the drug SA procedure has provided valuable insights into the brain substrates mediating volitional drug-taking behavior (45), which differ from one drug to another (46). Addictive drugs not only exert their reinforcing effects through activation of the mesolimbic dopamine system (47) where they hijack synaptic plasticity processes (48,49), such as long-term potentiation or long-term depression (50,51), but they also trigger various between-systems neuroadaptations (10,52,53) and changes in gene transcription and function, partly mediated by epigenetic adaptations (54–58). These adaptations occur in many brain systems (10), including the nucleus accumbens (Acb) (49,55,59), amygdala (60), dorsal striatum (61–65), and prefrontal cortex (52,66–69), with important effects on inhibitory control and stress responsivity (70,71).

PRECLINICAL MODELS OF RELAPSE

Extinction-Reinstatement Procedure

An influential advance in the development of preclinical models of addiction is the reinstatement procedure, initially suggested to model relapse in humans (15). Shaham's group and others greatly contributed to the refinement of this broadly used procedure, which is extensively reviewed elsewhere (72,73) and in the present issue. Reinstatement of instrumental responding, following extinction training, can be triggered by stress (74), the drug itself (22,75–77), the environmental context (15), and drug-associated CS (78,79).

At the neurobiological level, reinstatement of instrumental responding for addictive drugs has been associated with various structures of the corticostriatal circuitry, which include, but are not restricted to, the shell and core of the Acb and their glutamatergic afferents from the prefrontal cortex, the basolateral amygdala, and central nucleus of the amygdala (15). The neurobiological substrates of reinstatement depend on the drug and the procedure used to reinstate the response, such as stress, drug priming, contextual cues, and CS.

These cue-induced reinstatement procedures stem from the interaction between Pavlovian and instrumental processes (38). They often consist of a single instrumental session performed after extensive extinction training (typically 10–12 sessions) following short-term drug SA (10–12 days). Rats that had never been trained to seek cocaine (see following section for drug-seeking procedures), but have been trained to take cocaine on a low FR schedule, are exposed to this session during which each lever press results in a contingent presentation of the drug-associated CS. Instrumental performance during a reinstatement session reflects the acquisition of conditioned reinforcement (38), whereby the animal learns to lever press for the conditioned reinforcing properties of drug-associated CS in the absence of the drug. Cue-induced reinstatement assesses directly the motivational and reinforcing value of drug-associated stimuli. However, abstinence in humans occurs after protracted drug use, it is often voluntary and triggered by adverse consequences, and relapse is triggered by drug-related stimuli that have been extensively used by addicts as conditioned reinforcers.

Novel Models of Relapse: Self-Abstinence and Relapse in the Face of Adverse Consequences

New preclinical models of relapse have been developed (23,27,80) that more closely resemble voluntary abstinence