Pharmacology, Biochemistry and Behavior xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Review

Individual decision-making in the causal pathway to addiction: contributions and limitations of rodent models

Serge H. Ahmed

Université de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, 146 rue Léo-Saignat, F-33000 Bordeaux, France
CNRS, Institut des Maladies Neurodégénératives, UMR 5293, 146 rue Léo-Saignat, F-33000 Bordeaux, France

A B S T R A C T

The causal pathway from vulnerability to drug use and addiction involves a complex interaction between genetic, environmental, and behavioral factors. An individual can intervene on this causal pathway by two major types of individual decision. There is the inaugural, momentous decision to use a drug for the first time. This decision is influenced by both prior knowledge on the drug and its expected effects, and also by prior self-knowledge on one's own vulnerability. After an individual has used a drug for the first time, there is the decision to repeat drug use. This decision is influenced by the same factors that were involved in the inaugural decision to initiate drug use, except for one crucial difference. The first drug use has now acted on the individual, changing its brain acutely and also potentially persistently in a way that could bias subsequent decision-making in favor of repeated drug use. The goal of this review article is to assess the contributions and limitations of rodent models (i.e., rats, mice) to understand how prior drug use can influence decision-making in a way that favors future drug use. Overall, research on rodents shows that prior drug use can increase impulsive, risky and/or potentially harmful decision-making. However, this does not apparently translate into more drug use when rodents have the choice between a drug and a competing, nondrug option, except when the expected value of the latter is considerably decreased. The delayed drug reward hypothesis is developed to resolve and explain this apparent discrepancy. This novel hypothesis makes several unique predictions, some of them counterintuitive, and suggests that extrapolation of rodent research to humans should not only take into account differences in drug choice situations but also inherent species-specific differences in individual decision-making.

1. Individual decision-making in the causal pathway from vulnerability to addiction

The causal pathway to non-Mendelian disorders, including mental disorders, involves a complex interaction between genetic, environmental, and behavioral factors (Dick, 2011; Kendler, 2012). Among these disorders, even those with a strong genetic component depend for their phenotypic expression on prior exposure to environmental factors that are generally behaviorally evitable and/or escapable (Evans et al., 2011; Kendler, 2013; Willett, 2002). Provided that an individual is an autonomous decision-maker and is in possession of the relevant information, including information on his/her own vulnerability, before exposure to the relevant evitable factors, s/he can get protection from the disorder by deciding to avoid them. In theory, thus, there is always some elbow room for a vulnerable individual to change through his/her decisions the causal pathway to a non-Mendelian disorder (Kendler, 2013).

This seems to be particularly the case in the causal pathway to drug addiction where exposure to the main causal environmental factor, the drug, is largely a consequence of an initial individual decision. This is even truer for the very first decision to use a drug. It is indeed generally up to the individual, even adolescent, to choose to use or not a drug for the very first time. It is rarely the case that an individual is physically forced or coerced to use a drug for the first time. Even under persistent peer pressure and with easy drug availability, an individual's decision to use a drug for the first time is in the end up to him or her. S/he could have chosen otherwise (Foddy and Savulescu, 2006; Pickard, 2015; Vohs and Baumeister, 2009). No preexisting biological force or mechanism is compelling the individual to initiate drug use. This is not saying, however, that there is no preexisting factor that may bias individual decision-making toward initiation of drug use. These factors exist but none is sufficient alone or in combination to make the decision to use a drug for the first time inexorable (Belcher et al., 2014; Bickel et al., 2014; Casey, 2015; de Wit, 2009; Kendler et al., 2012; Swendsen and Le Moal, 2011).

What is less clear and more controversial, however, is what happens

E-mail address: serge.ahmed@u-bordeaux.fr.

http://dx.doi.org/10.1016/j.pbb.2017.07.005
Received 5 May 2017; Received in revised form 16 June 2017; Accepted 10 July 2017

after an individual has decided to use a drug for the first time. Now the drug has acted on the individual, changing its brain functions acutely and also potentially persistently in a way that could bias future decision-making in favor of more drug choice. Several researchers have hypothesized that addiction is largely a drug-induced decision-making disorder (Hyman, 2007; Keiflin and Janak, 2015; Lucantonio et al., 2012; Montague et al., 2004; Redish et al., 2008; Schultz, 2011). Accordingly, even if the initial decision to use a drug for the first time is up to the individual, such first drug use and subsequent one would induce a persistent dysfunction in the brain decision-making machinery that would bias choice toward repeated drug use. There is evidence for decision-making deficits in people with addiction (Bechara, 2005; Bickel et al., 2016; Biernacki et al., 2016; de Wit, 2009; Ekhtiari et al., 2017; Verdejo-Garcia et al., 2017). Notably, when probed in a laboratory setting and contrasted with healthy controls, people with addiction have been consistently shown to be more impulsive in their decisions and choices, mainly because of steeper discounting of delayed rewards, and also to make more risky decisions and choices which generally lead to disadvantageous consequences. Though not the only factors in addiction, impulsive and risky decision-making is nevertheless generally thought to represent an important contributing factor that biases choice, more or less selectively, towards repeated drug use over and at the expenses of other nondrug activities (Verdejo-Garcia et al., 2017). However, the process where an initially unbiased decision to use a drug leads to a biased decision toward more drug use has been difficult to test directly in humans, mainly because, all else being equal, it is not possible to test the causal effects of drug use on decision-making in an unbiased, controlled manner (Ekhtiari et al., 2017).

One way to approach this problem has been to resort to the use of animal models of decision-making. The main goal of the present review article is to summarize the contributions of and assess the limitations of animal research on the role of individual decision-making in addiction, with an exclusive focus on rodent models (i.e., rats and, to a lesser extent, mice). Research on nonhuman primates will be mentioned only briefly when relevant.

2. Two important individual decisions in the causal pathway to drug addiction

2.1. The inaugural decision to use a drug for the first time

There are fundamentally two important individual decisions in drug addiction. First, there is the decision to use a drug for the very first time. Importantly, this inaugural decision may be influenced by a host of different factors, personal and environmental, but not yet by prior drug use. Among the factors that may influence the inaugural decision to use a drug, there are, of course, an individual's prior knowledge about the drug and its expected effects, positive and negative, including even its addictive potential. This knowledge is generally socially transmitted, either by direct observation of significant others (e.g., a parent with drug addiction) or by socially-shared information (e.g., drug prevention information at school; drug information from peers) (Faupel et al., 2014). Another important factor is an individual's self-knowledge about his/her own vulnerability to develop addiction. Admittedly, this information is often hidden and difficult to acquire. However, individuals with a parent and/or a sibling who has developed drug addiction can generally acquire both a prior knowledge on addiction and its negative consequences, and, concomitantly, a prior knowledge about their own vulnerability (Kendler, 2013). There is evidence that many individuals who are highly vulnerable to drug addiction use this information to make a decision to never initiate drug use to live a life without drugs (Haller and Chassin, 2010; Harburg et al., 1982; Harburg et al., 1990).

Unfortunately, many other vulnerable individuals fail to make this momentous, potentially life-saving decision. Despite a prior knowledge on addiction and its negative consequences, and also a prior knowledge about their own vulnerability, they nevertheless make the decision to initiate drug use, thereby potentially setting the stage to the development of addiction. Briefly, one can envision several individual decision-making scenarios that are not necessarily mutually exclusive. First, the individual may decide, all things considered, including the risk of developing addiction, that a life on drug is better than a life without drug. Here the decision to initiate drug use is considered fully rational (Becker and Murphy, 1988). Second, the individual may also decide to initiate drug use, even knowing the risks, because s/he likes risk and expects to be lucky (i.e., risky decision-making). Third, the individual may decide to use a drug for the first time because s/he expects an immediate gratification and underestimates the long-term consequences (i.e., impulsive decision-making). Of course, many other decision factors are involved in the first drug use. However, because it is unique, this decision is delicate to capture and study in humans.

Could a rodent model help to contribute to address this question? It is important to handle this question at the outset of this review article as it reveals a potentially inherent limit of animal models. The inaugural decision to use a drug or not for the very first time cannot be modelled in a valid manner in rodents. This is mainly because when an animal, say a rat, is given for the first time an opportunity to self-administer a drug as a consequence of behaving in a certain way (e.g., by pressing a lever or nose poking a hole in a wall), it does not know in advance that its behavior will lead to drug delivery. Consequently, even if the behavior that causes an animal to get exposed to a drug for the first time is a voluntary act, it is not aimed at receiving a drug to experience its effects. On the contrary, the first drug use is always either forced or merely accidental (i.e., accidental from the point of view of the subject, not from the point of view of the experimenter who designed the experimental situation to increase the probability that this event will occur). Put differently, during the first drug use, the behavior and goal of the animal are not aligned with the resulting (albeit inadvertent) drug outcome. Thus, unlike people who always know what to expect, at least broadly, after they make the decision to experiment with a drug, the first drug experience is likely to be a total surprise for a rat or mouse. It is quite difficult to imagine what it is like to experience for the first time the effects of a drug, like cocaine or heroin, without any prior expectation.

In theory, one could try to reduce rodents' initial ignorance about the drug and its effects by designing an experiment where a drug-naïve animal is given an opportunity to observe the behavior of another animal – a cage mate, for instance – while it is actively self-administering a drug (Strickland and Smith, 2015). Under such circumstances, a rat will likely learn to expect that when its mate engages in a certain behavior, this leads to some other behavioral changes, such as, for instance, an increased locomotion or a variation in ultrasonic vocalization. However, it is not clear whether, how, and to what extent the observer will be able to infer any relevant information to make a decision to use the drug for the first time. Rodent models seem thus fundamentally limited to understand the decision factors that influence the first drug use. This explains why from now on, this review article will focus exclusively on the decision to repeat drug use after prior drug use or exposure.

2.2. The subsequent decision to repeat drug use

After an individual has used a drug for the first time, there is the decision to repeat drug use or not. This decision is likely to be influenced by the same factors that were involved in the inaugural decision to use the drug for the very first time, except for one major difference. The first drug use has now acted on the individual, changing its brain functions acutely and also potentially persistently. A multitude of drug-induced functional changes can be envisioned but, here, attention will be paid only to changes in individual decision-making that could bias choice toward repeated drug use. Among these changes, one can broadly distinguish between at least two major categories. First, there is