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Animal models of psychoactive drug use and addiction – Present problems and future needs for translational approaches

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ABSTRACT

Drug addiction is a psychiatric disorder based on a dysfunction of the brain. It frequently develops from a controlled drug consumption and drug instrumentalization (DI). Thereby, DI is the use of a drug to improve specific non-drug related behaviors, beyond the drug's direct positive or negative reinforcing effects. Currently available pharmacotherapies for drug addiction show low effect size and rather limited long-term efficacy, which suggests that current theories on addiction are still insufficient in how they capture the phenomenon and how they allow predictions for highly efficient treatments. This opinion review attempts a critical analysis of some aspects of current addiction neuroscience using animal models. As a result, (1) animal models that cover previously neglected types of drug memories in controlled drug use are suggested. (2) Animal models for drug instrumentalization are warranted. Animal models of drug addiction should consider that addiction develops predominantly in individuals with mental and/or environmental challenges. It is suggested (3) to preferentially use animal models with similar mental and environmental challenges to model the transition of controlled to compulsive drug use. (4) Animal models should in the future also capture the important aspect of the motivation to self-medicate in order to ameliorate a negative emotional/physical state. Potential pharmaco-treatments of addiction, in order to later achieve compliance in humans, should be tested for their systemic self-administration in order to self-medicate a drug-induced aversive state. This may allow a better understanding of the fundamental differences between an organism that shows controlled psychoactive drug consumption as an integral part of a 'normal' behavioral repertoire and one in a pathological condition with compulsive drug abuse.

1. Introduction

1.1. The problem of addiction

Human beings consume psychoactive drugs in virtually all societies and as long as record keeping for human behavior dates back [1,21,22,28,90]. In that, humans demonstrate the wish for altering their mental state for specific purposes. Other behaviors are performed in the drugged state, which are altered in their efficacy, or the altered mental state is just perceived as its own means end [62,63]. Zoopharmacognosy allows humans and other mammals to learn about these drug effects on mind and body, remember them, retrieve them when cued and to systematically use the expected result of the drug indulgence [33,52,81]. Although not a single known psychoactive drug appears as really necessary for human survival, psychoactive drugs can be efficiently instrumentalized for numerous purposes. Thereby, drug instrumentalization (DI) describes the highly systematic use of a psychoactive drug to facilitate other non-drug related behaviors. Those behaviors, also considered as instrumentalization goals, include, e.g., the facilitation of social interactions, the facilitation of sexual/mating behavior, coping with stress, coping with psychiatric disorders, and cognitive enhancement [62,63,65]. In human DI, drugs act in a much more complex, but also economically efficient way than their direct positive/negative reinforcing action would suggest. In that, DI may explain the highly systematic integration of psychoactive drugs in many life routines of controlled drug users [62,63,65].

Despite of their DI, virtually all natural as well as synthetic psychoactive drugs have significant downsides. First, they can be potent toxins [24,68,91], which means that there is a dose range, in which the drug has acute deleterious effects on the integrity and/or function of the bodies' organ systems. For numerous psychoactive drugs this range overlaps or is very close to the dose range of the desired effects. Besides acute toxicology, another problem arises from repeated consumption. Even if the consumption occurs in an acute non-toxic range, organ systems, specifically the brain, adapt to the presence of the drug and become dysfunctional when the drug is washed out [27]. The

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behavioral systems of the brain also adapt in a way to organize a repeated self-supply of the drug. These effects can escalate in a circular manner, thus, inducing neuroadaptations in behavioral systems together with an escalated intake of the substance [29,38]. The consequence is that the behavioral repertoire of the organism becomes more and more limited and inflexible. Other organ systems also become increasingly dysfunctional up to a level when organ failure may cause death [63]. Importantly, what was once a behavior of free choice in the drug user becomes increasingly compulsive. Free choice seems no longer possible. Instead external and interoceptive cues inevitably drive drug seeking and taking behavior [6]. These consequences of psychoactive drug consumption are classically captured as “drug abuse” and “drug addiction” and are acknowledged to be a psychiatric disorder with a brain dysfunction at its core [40,48,99].

Numerous epidemiological surveys outline the range of the problem at a world-wide scale [23,82]. Together with mental and neurological disorders, substance use disorders accounted for 10.4% of global disability adjusted life years and 28.5% of years lived with a disability in 2010 [105,106]. A single drug, like alcohol was estimated to account for 3.8% of all global death and 4.6% of global disability adjusted life-years [75]. It is commonly agreed that drug abuse as well as addiction cause not only problems to the individual who has at least once voluntarily initiated the consumption. Also the immediate and extended social environments of those individuals suffer a great deal. There are now calculations that approach the problem also in financial terms and estimates on how much addiction probably costs a society [75,109]. For example, the costs of alcohol amount to more than 1% of the gross national product in high-income countries [75]. Arising from the individual suffering and the economic damage to society, there is a profound wish to prevent the occurrence of addiction and to treat it efficiently once it established.

1.2. Why using animal models of addiction?

Given that addiction is always bound to drug availability, the wish to abruptly put an end to all drug consumption by simply reducing availability or prohibiting them is, at least in theory, a highly plausible approach, that does not apply to any other psychiatric disorder. History has shown that a reduction may work, but complete elimination of culturally deeply rooted drugs, such as alcohol in western societies, frequently failed [28]. If that is not possible, the next best option may be the prevention of drug use escalation to addiction. In fact, most of the regular users of psychoactive drugs are not addicted by clinical diagnostic criteria, and will never become such in their lives [17,30,100]. This shows that psychoactive drugs can be controlled by humans relatively well when total numbers are considered. However, at individual level this does not help. After acknowledging addiction as a true disease with an organic base, rather than a disorder of will-power, an evidence-based treatment for this medical condition is warranted. Since proposed treatments had to be tested before being applied in addicted patients, there was a need for appropriate test systems. These systems should be accessible in an ethically acceptable way and should have predictive power for patients. Findings in these systems should be readily “translatable” to patients and lead to an effective remedy. At the nodal point between ethical access and translatability are animal models. Treatments can be tested with less ethical restrictions. At the same time, neurobiology has shown that in particular mammals share the major morphological and biochemical principles of how their brains work. In particular rodent models add the value of cost-effectiveness: a high number of single tests can be performed at reasonable costs for society [70,83,86].

Together with the wish to test potential treatments for addiction, there grew the wish not to test by trial-and-error, but to predict effectiveness beforehand. This requires a theory of addiction which delivers predictions on treatment efficacy. After it was agreed to be a disorder of the brain, the core of an addiction theory had to be a theory of the brain. The wish to generate such a theory and design and predict treatments constitutes another major reason for animal models of addiction. In parallel to neurobiological research, which has long been using animal models for the creation of theories for principal brain function, addiction research used similar models to develop a neurobiological theory of the pathological brain processes underlying addiction [39,108].

The present article attempts to provide a critical summary of how far these demands had been met by animal models of addiction. It will not focus on the neurobiological features of current addiction theories or pharmacological approaches to treat addiction as this is done in detail elsewhere [53,64,87], but analyze how available animal models have served these tasks. It will be discussed what type of treatments and addiction theories animal models have provided so far. In a next step, reasons for the currently observed “translational failure” will be identified and suggestions for future improvements will be elaborated.

2. Current status of addiction treatment

Regular consumers of addictive drugs often feel no need for a change and no need of treatment. They even deny that there are problems arising from the drug consumption [101]. A smaller proportion of them and/or their social environment is aware of the problems arising from consumption and wish for a change of their condition. Those consumers fall in two categories: those who are self-adjusting their problematic behavior and those who recognize that they are no longer able to efficiently control it. Those with a loss of control over their habit may present at treatment institutions for a qualified withdrawal and/or management of abstinence. While the acute withdrawal from virtually all psychoactive drugs can now be managed in a satisfactory way, long term abstinence or remission to controlled consumption is for many addicted drug users difficult to achieve. Although pharmacotherapies for the addiction to some drugs, like, e.g., alcohol and nicotine, made significant progress in the last decades [41,111], they are still limited to some drugs and patient subpopulations, and show in general a relatively small effect size [36,57]. In fact, relapse rates in the clinic are very high and scientific scrutiny of the actual therapeutic success in well-controlled studies yields rather poor rates, even if there are exceptions at single case level [11]. This is much in contrast to the predictions made by addiction neuroscience theories. Over the last decades, a great number of treatment targets had been proposed [53,61,87]. These promises arose from the discovery of signaling molecules in the brain that were found to be essential to establish and express addiction-related behaviors in animals. For many of these targets converging evidence was obtained in that not only one model in a single species found them essential for drug-related behavior, but several models in animal species [31,64,88]. Marketable and reasonable safe compounds were developed and tested in human trials. Either in this phase of validation or later in clinical practice, many proposed pharmacotherapies of addiction failed and left clinical practice with only a handful of treatment options restricted to only some addictive drugs [53,87,111].

3. Current status of drug use- and addiction theories

Addiction is a disorder of the brain with largely unmet treatment needs. This suggests that our understanding of the phenomenon, reflected in the theories of drug consumption and addiction, may not be sufficient yet. But what do we want from these theories? No more than from other theories too: they should provide a logical system of explanation for the phenomenon. Structurally, this means they are a system of ‘if A – then B’ ($A \supset B$) relationships that link as many observations in a logical stringent way as possible. A single connection would have the structure of e.g. “If a substance increases dopamine (DA) levels in the shell of the nucleus accumbens (Nac), then it triggers the establishment of self-administration behavior”. One nature of these