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Review Article

Animal Models of Addiction

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Abstract

The growing increase in the consumption of illicit products (heroin, cocaine, ecstasy), addiction and problems with withdrawal linked to the administration of substances acting at the central level (benzodiazepines, antidepressants, barbiturates, etc.) require early management of addictive activity of molecules. The acquisition of behavior self-administration was then studied as an animal model initiation of addiction and the resumption of this behavior after its extinction as an animal model of relapse or "Craving". In fact, the discovery of rewarding effects of drugs in non-dependent animals does not have not just relegated addiction physics in the background in the definition of addiction but it's also contributed to elude conceptions and descriptions psychiatric the notion of "individual personalities vulnerable". For the first time, the experimenters - mainly neurobiologists - sought to develop new theories of addiction based mainly on knowledge of neurobiological substrates rewarding effects drugs. Knowledge of neuronal mechanisms and structures involved in these phenomena in animals is of great benefit in terms of research strategy, and makes it possible to guide the choice of criteria for evaluating possible drug dependence in clinical trials. Reliable and reproducible animal models, allowing rapid detection of drug dependencies during development should be implemented.

Keywords: Drug self-administration; Face validity; Predictive validity; Animal models; Drug addiction; Withdrawal; Substitution

Introduction

The study of the causes and neurobiological mechanisms of addiction requires the use of animal models [1]. This use of animals can be justified for several reasons. First, ethics prohibits the use of invasive neurobiological approaches in humans. Second, there are no alternative mathematical or in silico models of addiction yet. Finally, unlike physical dependence, addiction is a behavioural disorder and, as such, cannot be summarized on human or animal cells or any other in vitro, cellular or subcellular model. Research on animal models therefore represents a kind of "reverse medicine", call now translational medicine. Unlike the clinician whose goal is to help addicted people avoid it, the experimenter seeks to reproduce certain aspects of addiction in laboratory animals considered a priori healthy. Since the very first systematic experimental studies in animals in the 1950s, animal models of addiction have evolved considerably, in close connection with the very conceptions of addiction [2]. To simplify, we can distinguish three major periods of experimental research on animal models of addiction, each involving researchers from different backgrounds (pharmacologists, psychologists, neurobiologists and psychiatrists) and referring to particular conceptions of the phenomenon [3]. These three periods are preceded by a pre-scientific period, before 1950, during which, no systematic attempt was made to model addiction in animals, while animal experiments in physiology and psychology were in full swing. More recently, increasing attention has been paid to the risks and possibility of chronic dependence and abuse of centrally acting substances, such as hypnotics, barbiturates, benzodiazepines, and even other psychotropic medications such as antidepressants and psychostimulants [4,5]. Now is the time to more clearly define the protests of central and peripheral dependence and understand how substances affect neurobiology and behavior in both humans and animals. In addition, the problems of consumption of illicit products such as heroin and its derivatives, cocaine, as well as new substances such as methamphetamines, the most consumed being ecstasy, unfortunately remain relevant. Faced with this situation, it is essential to have reliable and reproducible animal models. Preclinical studies allow us to deepen our knowledge of the neuropharmacological bases of the action of substances and to understand the mechanism and pathways involved in drug consumption. Interaction studies allow the evaluation of molecules capable of attenuating or eliminating the self-administration of medications or drugs in animals, which is a great advantage compared to humans [6].

Self-Administration

The objective of self-administration studies is essentially to highlight the addictive potential of a given substance and to study its effects on behavior [7]. The procedure allows early detection of addictive potential, which is necessary during the development of a molecule for therapeutic purposes. In addition, the protocol can be used for different classes of products and validated statistically. In self-administration studies, products are used as positive reinforcement to maintain drug-seeking behavior [8]. Usually, self-administration procedures use operant conditioning models. In these conditioning studies, animals are placed in soundproofed and ventilated experimental cages (Skinner boxes). A feed trough is accessible on one of the walls of the cage where the animal can feed in the form of easily countable pellets. The animals have a lever that they must press to receive the food. This food is considered positive reinforcement [9]. In addition, each cage has lights that can be used independently (discriminating stimulus). A sound device may also be usable. In self-administration studies, the products are used as positive pharmacological reinforcement in place of food. We then observe a rapid development of physical dependence. Animals can obtain the drug in different ways: in most experiments, drugs are obtained using chronically implanted catheters during brief

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surgical anesthesia; non-invasive methods with oral administration can also be used [10]. In monkeys, a procedure involving intramuscular administration was used, involving greater ease and allowing chronic administration over a long period; however, the effects are weaker than those of intravenous administration [11]. There are inhalation techniques allowing the study of volatile drugs (tetrahydrocannabinol, nicotine). Two procedures allow us to study the localization of the reward mechanism induced by a drug. One is intracranial self-administration; the other is the conditioned place preference procedure. Intracranial microinjections offer the possibility of localizing the brain systems involved, as opposed to peripheral administration, which certainly allows the study of a wide range of drugs, but does not allow localization of the site of action [12]. The experimental problem remains the injection of small volume without altering neighboring structures. There is a good correspondence between drugs that maintain self-administration in laboratory animals and those that are used in humans for addiction purposes [13]. The animals used for these studies include monkeys (rhesus monkey or baboon), rats which are trained to press a lever using their snout. Rats are the most interesting, because they have a lower cost, allowing the use of animals naïve to the drug studied, the use of a single protocol and a correct statistical analysis [14]. Compared to rodents, monkeys present many problems including maintenance problems. This test is sensitive to psychostimulants such as amphetamine and cocaine, opiates such as morphine and heroin, phencyclidine, barbiturates, benzodiazepines, ethanol, nicotine and some volatile solvents [15]. There are exceptions for cannabis, which gives equivocal results, and LSD, which gives negative results. In the majority of cases, no false and not in others, depending on the dose used, the history of the animal and the conditions of access to the drug [16]. Cocaine is often used as the standard comparison substance in these studies. In conclusion, it is above all a question of evaluating a physical dependence more than a psychological dependence; it is necessary to be vigilant about the quantity of food administered to the animal during the experiment, which largely conditions the response, it is thus possible to artificially increase the potential for "dependence" by reducing the quantity of food made available to the animals.

Discrimination

The goal of discrimination studies is to evaluate the psychological dependencies of a substance [17]. Maintaining the behavioural sensation induced by the product also makes it possible to determine whether a product belongs to a class or to study the effect of different doses. The fact that substances induce discriminative control behavior is a phenomenon of practical and theoretical interest. Operant conditioning procedures are also used in discrimination studies, but two levers are then necessary [18]. Other drugs are then injected to determine if they also cause a response controlled by the training drug, this is called generalization. In conditioning studies, it is usually a light or sound that is used as discriminative stimuli or as signals controlling behavior. In discrimination studies, substance effects are used as discriminative stimuli indicating how much reinforcement (number of pellets) can be obtained. Animals are trained to press a lever to obtain food after administration of a potentially addictive agent and to press a second lever in the presence of a sodium chloride solution (placebo) [19]. When the discrimination is assimilated, the animals press the appropriate lever depending on whether they received the training substance or the saline solution. Accuracy is excellent in most experiments (90% or more satisfactory answers). Studies using opioid substances as carriers have revealed excellent molecular specificity, and even stereospecificity. Most substances with addictive properties such as psychostimulants, benzodiazepines and LSD also have discriminating effects [20]. These effects are important in drug addiction. Indeed, one of the reasons why humans abuse drugs is the need to obtain subjective effects characteristic of the substance consumed. For example, substances that produce the same discriminatory effects as morphine in animals are also those that produce effects similar to morphine in humans [21]. The discrimination procedure therefore appears to offer experimental access to the perception or stimuli produced by drugs [22].

Withdrawal

Withdrawal allows physical dependence to be unmasked, thus reflecting an adaptive process of administration of the substances studied [23]. There are two main types of withdrawal [24]:

Spontaneous withdrawal: a phenomenon of dependence is induced by the chronic administration of a product for a more or less long time, then the administration is suddenly stopped. We then note the time of appearance of the first signs of withdrawal, their intensity and their duration [25].

Precipitated withdrawal: this involves the induction of withdrawal by administration of an antagonist of the receptors occupied by the substance. After chronic administration of a substance, its antagonist is administered to the animal, thus precipitating its withdrawal. For example, administration of naloxone for opioid withdrawal or administration of flumazenil for benzodiazepines [26].

The signs of withdrawal are then assessed using behavioral grids. For example, signs of benzodiazepine withdrawal are generally divided into three criteria [27,28]:

- motor effects (tremors, convulsive movements, reduction of spontaneous motor activity, tail erection, arched posture);
- autonomic nervous system (piloerection, diarrhea, white ears);
- behavior (anxiety, aggressiveness, increased startle to an auditory or tactile stimulus).

These withdrawal symptoms have been well studied in animals and humans; they are common upon sudden cessation with some minor variations [29]. For opioids, it is possible in rats to quantify compulsive jumping, leg shaking, grooming, burrowing and twisting behaviors, and diarrhea [30].

Substitution During Withdrawal or Cross Dependence

These studies are based on the hypothesis that a substance capable of to suppress the withdrawal syndrome when stopping another substance is likely to produce the same type of addiction. Some techniques used should be compared to those of "self-administration" studies [31]. The animals are placed in soundproofed experimental compartments (see Self-administration) and have a lever. They are trained according to a specific strengthening program and self-administered the benchmark drug. In other techniques, the animals passively receive the substance. In these

cases, signs of withdrawal are analyzed after substitution [32]. This principle of cross dependency is used either for substitutions of doses for the same molecule, or for substitutions of different substances. There may be substitutions partial in which the substitute substance only partially eliminates the withdrawal syndrome of the other molecule.

Conditioned Place Preference

In conditioned place preference studies, an environment distinctive is repeatedly linked to the administration of a substance, and another environment is connected with failure to take the product [33]. Traditionally, the device consists in a box divided into two separate compartments (or chambers). A guillotine separates the two compartments. Each to record the time and detect the movements of animals. This system can be connected to a computer. A recording video can also be set up. The boxes are then placed in a soundproof system and under a weak white light [34]. The rat is the animal of choice, but study in mice is also possible. Typically, environments differ by visual signals (illumination, light or dark walls, painted in black and white, vertical lines or horizontal), tactile signals (soil texture: soft or rough) and sometimes by the smell. After training by confinement in the compartment allocated either to the drug or to placebo, the animals regain free access to both compartments. The usual measurement parameter used is the increase time spent in the compartment associated with the drug. This test has been used successfully with a wide range addictive drug that also maintain self-administration. There are, however, a few exceptions: phenobarbital and phencyclidine [35]. It is an alternative technique of self-administration procedures. As we had it mentioned in the first paragraph, this technique also allows the study of the location of mechanisms involving reward circuits thanks to the possibility of microinjections at the level of brain structures (see Self-administration).

Awakened Animal Microdialysis and Free of Its Movements

This technique allows the study of animal behavior and the quantification of transmitters released in brain regions [36]. Briefly, the technique is broken down as follows: the animal is anesthetized and placed in a stereotaxic apparatus. A guide for the microdialysis cannula is then implanted in the desired region using stereotaxic coordinates. Then we let the animal recover from the surgery. Five to seven days later, the microdialysis probe is placed and infused with physiological saline. The drug studied is in turn administered by this probe. The dialysates are recovered and analyzed.

Models to Invent

Research on animal models has come a long way over the past 60 years. However, several obstacles remain to be overcome in order to improve its validity. First, we must strengthen the return to the clinic, the subjective symptoms of addiction seem still escape animal models. For example, the desire to limit consumption or to abstain is undoubtedly one of the most important symptoms because without this desire, there is no motivational conflict or attempt at abstinence and therefore compulsion. In fact, there is not yet an animal model of abstinence. Second, laboratory animals generally have access to drugs without any other option. It is therefore difficult, if not impossible, to know whether they use the drug addictively or only because of the lack of other options [37]. Future research on addiction models should introduce, during drug access, other activities that are biologically and / or socially important for the animal being studied. The abandonment of the latter for drugs and the costs it entails in terms of health and well-being would be a particularly valid model of addiction. Finally, most models adhere to a simplistic etiological hypothesis that attributes a central role to prolonged drug exposure, a hypothesis that largely ignores the multifactorial etiology of addictions [38]. Some animal models still have to be invented.

Conclusion

Determining the addictive potential of a substance can be made using animal models. It should however to be careful to avoid false negatives (addictive substances in men who have not revealed their addictive potential in animals), but also false positives. In either case, the experimental design is important; do not reduce the animal's food too much under penalty of making him more quickly dependent, or on the contrary feed him too well so that he no longer wants to do efforts. The assessment of marketing authorization files must therefore be careful in regarding psychotropic drugs, and the expert should refer to source files. In case of doubt, a second opinion should be performed by an independent laboratory. Finally, a single model cannot be retained; it is right to compare the results of the five models proposed here in order to make a preclinical opinion.

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