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Invited review

Environmental modulation of drug taking: Nonhuman primate models of cocaine abuse and PET neuroimaging

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ABSTRACT

The current review highlights the importance of environmental variables on cocaine self-administration in nonhuman primate models of drug abuse. In addition to describing the behavioral consequences, potential mechanisms of action are discussed, based on imaging results using the non-invasive and translational technique of positron emission tomography (PET). In this review, the role of three environmental variables – both positive and negative – are described: alternative non-drug reinforcers; social rank (as an independent variable) and punishment of cocaine self-administration. These environmental stimuli can profoundly influence brain function and drug self-administration. We focus on environmental manipulations involving non-drug alternatives (e.g., food reinforcement) using choice paradigms. Manipulations such as response cost and social variables (e.g., social rank, social stress) also influence the behavioral effects of drugs. Importantly, these manipulations are amenable to brain imaging studies. Taken together, these studies emphasize the profound impact environmental variables can have on drug taking, which should provide important information related to individual-subject variability in treatment responsiveness, and the imaging work may highlight pharmacological targets for medications related to treating drug abuse.

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1. Introduction

Drug abuse continues to be a major public health problem worldwide (WHO, 2004). Recent estimates report between ~4 and 6% of those surveyed (ages of 15–64 yrs old) used some illicit substance in 2008 (UNODC, 2010). In the United States approximately 22 million people reported drug use, of which ~1.6 million were cocaine users (SAMHSA, 2010). In Europe, the number of reported cocaine users doubled in the last decade (UNODC, 2010). Despite significant advances in our understanding of the behavioral neuropharmacology of drugs of abuse, successful and sustained treatment strategies, especially for stimulants like cocaine, have not been discovered.

While there are many variables mediating drug taking, in the simplest terms, these could be organized within three general categories: agent, host and environment (O'Brien, 2011). For this review, the primary "agent" we will consider is cocaine, although, it is our belief that the principles described would apply to behavior maintained by other abused drugs, such as methamphetamine and nicotine. The "host" refers to the individual. It is a hallmark of addiction that there are individual differences in response to drugs; a particular advantage of animal models is that these behavioral phenotypes can be systematically and explicitly studied. Finally, "environmental variables" can include alternative reinforcers, social context and punishment; these also can be systematically studied in animal models. While social rank could be considered a host (i.e., organismal) variable, we will consider it as a result of the social environment and treat it as another environmental manipulation. The goal of this review is to highlight the powerful role the environment has on cocaine self-administration in preclinical models, primarily those involving nonhuman primates. Several environmental variables will be examined, including alternative reinforcers, social factors, and punishment. We will also describe in vivo imaging studies that help elucidate the mechanisms of action for these various environmental variables. The aim of this review is to address whether different environmental manipulations that increase or decrease cocaine-maintained behaviors in preclinical models produce similar changes in the brain as measured using in vivo imaging techniques.

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1.1. Models of cocaine self-administration

There are several excellent reviews of the use of conditioned and unconditioned behaviors to assess cocaine reinforcement in animals (e.g., Griffiths et al., 1980; Woolverton and Nader, 1990; Koob et al., 1998; Ator and Griffiths, 2003; Banks and Negus, 2012), so this section and subsequent sections will not be exhaustive. Rather, we will focus on the animal models that will be highlighted in this review, which involve cocaine self-administration procedures. Animals will self-administer many of the same drugs that humans abuse and by the same routes, with strikingly similar patterns of intake (Deneau et al., 1969; Griffiths et al., 1980; Ahmed and Koob, 1998, 2005). If responding leading to the presentation of the drug occurs at higher rates than vehicle-maintained responding, the drug is said to function as a positive reinforcer and may have abuse potential. When studying reinforcing effects – i.e., determining whether the drug injection maintains higher rates of responding than vehicle-contingent responding – the most frequently used simple schedule of reinforcement is the fixed-ratio (FR) schedule. Under FR contingencies, the consequent stimulus is delivered following a specified number of responses. Under these conditions, responding is characterized as an inverted U-shaped function of dose (see Pickens and Thompson, 1968; Skjoldager et al., 1991; Zernig et al., 2004).

Measures of reinforcing effects using simple schedules of reinforcement do not allow for direct comparisons between reinforcing stimuli (Woolverton and Nader, 1990). For this purpose, models of reinforcing strength, such as progressive-ratio or concurrent-access choice schedules of reinforcement are frequently implemented. For this review, we will focus on choice paradigms and, in most studies the choice was between cocaine and a non-drug alternative, food (see Banks and Negus, 2012 for a recent review). One of the rationales for food-drug choice studies is the goal of reallocating choice from cocaine to a non-cocaine alternative (Banks et al., 2013). From a translational approach, this model has perhaps the strongest predictive validity to the human condition.

Since Dews (1955) classic study, behavioral pharmacologists have been aware of the powerful role the environment plays in drug effects, including drug self-administration. In this review, we highlight methods that have been shown to increase or decrease drug self-administration in nonhuman primate models: alternative reinforcers, social factors and punishment. We describe the strengths and weaknesses of each approach and we delve into the potential neuropharmacological mechanisms for each, using non-invasive brain imaging protocols (described in the next section). The goal is to highlight how different environmental events that alter cocaine self-administration do so via similar or different neuropharmacological mechanisms.

1.2. Brain imaging protocols in nonhuman primate models

There are several excellent recent reviews involving nonhuman primate imaging studies (Howell and Murnane, 2011; Murnane and Howell, 2011; Gould et al., 2012, 2013). Most of the imaging studies described in this review utilized positron emission tomography (PET), although we do mention other imaging modalities, including those based on magnetic resonance imaging (MRI) (see Nader and Czoty, 2008 for additional imaging rationale for studies involving nonhuman primates). PET imaging involves positively charged subatomic particles (i.e., "positrons") that travel in space (for this review, the space is the brain) in a random fashion until they collide with electrons and are annihilated. The result is gamma particles that project at 180° with an energy of 511 keV (i.e., "emission"). PET cameras have detectors that recognize stimulation at 180° and provide information about the location of annihilation in 3D (i.e., "tomography"). The most frequently used radioactive tracers for receptor-based PET studies are ^{11}C (half-life of 20 min) and ^{18}F (half-life of 110 min). Glucose utilization is assessed using ^{18}F fluorodeoxyglucose ([^{18}F]FDG). Data are analyzed for a specific region of interest, although whole brain analyses of metabolism and blood flow can also be analyzed, and the distribution volume (DV) is compared to a reference region. The ratio of DV values is the primary dependent variable (referred to as the distribution volume ratio, DVR). It is a unit-less number that reflects receptor availability. Another common dependent variable is the binding potential and this number too reflects both affinity (*Kd*) and the receptor number (*Bmax*).

Many studies use the same PET camera and receptor-based radiotracer in animals and humans, making PET imaging a highly translational research technique. However, one major difference is that the majority of preclinical imaging studies anesthetize the animal prior to and throughout the PET study, while humans are typically studied awake. Although some investigators have conducted awake imaging in monkeys (e.g., Howell et al., 2001, 2002; Murnane and Howell, 2010), depending on the research question, it is not always necessary to use conscious, behaving monkeys in PET imaging studies (see Nader and Czoty, 2008 for additional information). For example, if an investigator is interested in correlating receptor availability, as a trait measure or after some manipulation (a state measure), with some behavioral outcome, using anesthetized subjects can address those research questions. The preclinical studies described in this review only used anesthetized subjects.

2. Alternative reinforcers and cocaine self-administration

While preclinical laboratory studies investigating drugs as reinforcers typically utilize simple schedules of reinforcement, drug vs. non-drug choice procedures have become the standard in clinical studies of drug reinforcement (Haney and Spealman, 2008; Banks and Negus, 2012). Furthermore, interest in drug reinforcement is derived from its presumed role in drug addiction, and drug addiction can be defined as a disorder of choice and behavioral allocation (Heyman, 2009; Hernstein and Prelec, 1992). Moreover, in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, six of the 11 diagnostic criteria for substance dependence are defined as inappropriate behavioral allocation towards the procurement and use of the illicit substance. Thus, drug addiction implies excessive drug choice at the expense of more adaptive behaviors and increased preclinical use of choice procedures might facilitate translational research in the development of effective treatment strategies.

2.1. Behavioral effects of environmental variables using cocaine-food choice paradigms

There are several outstanding reviews on the use of choice paradigms in drug addiction research (e.g., Bergman and Paronis, 2006; Banks and Negus, 2012). We will focus on a few experiments that are relevant to imaging studies described in the next section. In one of the first intravenous drug vs. non-drug choice procedure, rhesus monkeys were given a choice between cocaine injections (0.3 mg/kg per injection) and food (five 1.0-g banana-flavored pellets) under conditions in which no other source of food was available outside of the choice procedure (Aigner and Balster, 1978). Over the 8 experimental days, monkeys almost exclusively chose cocaine over food despite body weight losses of 6–10%. Specifically, the use of choice procedures in nonhuman primates allowed for the assessment of this excessive behavioral