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Animal models of addiction

Reward comparison: the Achilles' heel and hope for addiction

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In the words of the late Charles Flaherty, reward comparison is commonplace. Rats and humans, it appears, compare all rewards and this capacity probably contributes to our ability to select the most appropriate reward/behavior (food, water, salt and sex), at the most ideal level (e.g. a certain sweetness), at any given time. A second advantage of our predisposition for reward comparison is that the availability of rich alternative rewards can protect against our becoming addicted to any single reward/behavior. Thus, the potential protective effects of natural rewards/enrichment are addressed. Despite this, behavior can become inflexible when, through the development of addiction, stress, drug or cues elicit craving, withdrawal, and ultimately, drug-seeking. Drug-seeking corresponds with a 'window of inopportunity', when even potent natural rewards have little or no impact on behavior. During this time, there is a unitary solution to the need state, and that solution is drug. The present animal model explores this 'window of inopportunity' when natural rewards are devalued and drug-seeking is engaged and considers a mode of possible intervention.

Addiction: the magnitude and nature of the problem

According to the figures provided by the National Institute on Drug Abuse http://www.nida.nih.gov/Infofacts/index.html, in 2004, 34.2 million Americans used cocaine at least once, 7.8 million Americans used crack at least once, 2.4 million Americans used heroin (87% under the age of 26), and there were 450,000 current users of ecstasy. There were 14.6 million users of marijuana in 2004 and 70.3 million Americans smoking cigarettes. These large numbers are even more problematic because many individuals become addicted and addiction, more often than not, is not resolved following even extended periods of abstinence. In fact, addiction is a disease of chronic relapse [1], which costs society an estimated $484 billion dollars/year as the addict repeatedly cycles from addiction to abstinence, withdrawal, drug-seeking and relapse. Clearly, recovery of even part of these dollars through the successful treatment of the disease would constitute quite an economic stimulus package.

Along with society, the addict and his or her family also are adversely affected because addiction is associated with an apparent devaluation of, and inattention to, natural rewards. According to DSM-IV, substance abuse and dependence involve a failure to fulfill major obligations at work, school or home, the giving up of important social, occupational or recreational activities, and continued drug use despite recurrent physical, legal, social or psychological problems. This categorization is substantiated by published data showing that the human addict weighs less, is more often absent from work, fails to respond appropriately to monetary rewards, and more often has his or her children removed from the home because of neglect [2–5].

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Natural rewards: potential for hope

Although it is the case that drug-induced devaluation of natural rewards is an Achilles' heel for the addict and devastating for his or her family, it also is true that natural rewards may be the addict's best natural defense against substance abuse, addiction and relapse. For example, Higgins *et al.* [6] have shown that abstinence is greatly improved when human drug addicts are given the opportunity to 'work' for (i.e. to stay abstinent for) tokens to purchase canoes, bicycles or college credits, for example. The key, then, is to understand the conditions under which drugs devalue natural rewards and, alternatively, the conditions under which natural rewards might serve to protect against substance abuse and addiction. To this end, we continue to hone the first animal model for the systematic study of drug-induced devaluation of natural rewards [7,8]. We will describe this model and discuss what has been learned about devaluation, drug-taking and the potential protective effects of natural rewards on substance abuse, addiction and relapse.

The model: experimenter delivered drug

Since the mid-1950s it has been known that rats avoid intake of a gustatory conditioned stimulus (CS), such as saccharin, after it has been paired with an aversive, illness-inducing agent such as lithium chloride (LiCl) or X-radiation [9–11]. This phenomenon, referred to as a conditioned taste aversion (CTA), was found to occur following a single taste-illness pairing and even when using relatively long intervals between access to the CS and exposure to the aversive unconditioned stimulus (US). As such, the phenomenon generated a great deal of controversy because it challenged then basic principles of animal learning theory.

It was amid this controversy scientists discovered that not only putatively aversive agents, but also drugs of abuse, suppress intake of a gustatory CS following repeated taste–drug pairings [12]. Effective drugs include morphine [13–15], cocaine [16], amphetamine [17], ethanol, flurazepam, chlordiazepoxide [14,18,19], nicotine [20], amobarbital and phenobarbital [19] and heroin [21]. Rats, then, avoid intake of a taste cue following pairings with not only LiCl, but also all drugs of abuse tested, across a range of doses [22], when administered intraperitoneally (ip), subcutaneously (sc), intravenously (iv), and even, in some cases, when administered directly into the nucleus accumbens [17,23–26].

Given the climate, this phenomenon also was interpreted, almost immediately, as a CTA [18]. Even so, it was viewed as highly paradoxical that such drugs, drugs that were readily self-administered by rats and humans [27], also evidenced aversive properties in the CTA paradigm. Indeed, in three key experiments, avoidance of the taste cue was found to be accompanied, in the exact same study, by faster running for the drug [28], more time spent in the drug-paired compartment in a conditioned place preference task [29], and avid self-administration of the drug [24]. Since this time, additional evidence has been generated to show that addictive agents have aversive properties [25,30,31] and the aversive response to the taste cue following taste–drug pairings has been attributed to a range of factors including stimulus novelty, drug shyness (i.e. fear of novel drug or drug-induced state), fear [32], and positive conditioned suppression (i.e. a phenomenon where responding is suppressed by stimuli that precede the response-independent presentation of shock or food, e.g.) [33–36].

While it is the case that rats clearly avoid intake of a taste cue when paired with a putatively aversive US, such as LiCl, for example, Flaherty and Checke [37] reported that rats also avoid intake of a saccharin CS when paired, once in daily sessions, with a highly preferred 32% sucrose solution. This phenomenon was referred to as an *anticipatory* contrast effect because reduced intake of the saccharin cue was thought to be due to anticipation of the availability of the preferred sucrose reward in the very near future. Indeed, in a subsequent within-subjects study, it was shown that the reduction in intake of the taste cue depended upon the value of the 32% sucrose reward anticipated in the near future, not upon the memory of the 32% sucrose solution received 24 hours earlier [38]. Anticipatory contrast effects, then, depend upon the development of a Pavlovian associative relationship between the saccharin CS and the sucrose US [39] and the lesser reward CS is avoided in anticipation of the imminent availability of the preferred reward US [39,40].

Given this information, we hypothesized that rats avoid intake of a drug-associated taste cue because the value of the taste cue pales in comparison to the powerful drug reward anticipated in the very near future [7]. By way of indirect support, a great deal of data suggest that drugs of abuse are rewarding and that drug-induced suppression of CS intake is not like that induced by LiCl. Specifically, drugs of abuse are readily self-administered (for review, see [27]) and they support the development of conditioned place preferences [41–44]. Unlike drugs of abuse that support a reduction in CS intake, but an increase in instrumental responding (as described above), LiCl suppresses both consummatory and instrumental responding [24,28,29]. Rats do not work for LiCl. Finally, as discussed previously [45], Parker [22,46–49] used the Taste Reactivity test [50] and showed that intraoral delivery of a LiCl-paired CS led to both a decrease in ingestive responses (e.g. tongue protrusions, paw licking and mouth movements) and an increase in active rejection responses (e.g. gapes, chin rubs and paw treading). The intraoral delivery of a drug-associated CS, on the contrary, led to a decrease in ingestive responses, with no clear increase in active rejection responses [46–48,51].

Dissociations of this nature argued against a CTA account, but did little to address the potential merits of the reward comparison hypothesis. To this end, we reasoned that if the