# Pavlovian Psychopharmacology

**Monitor, 2004, 35(3): p18, American Psychological Association**

New research suggests that, in response to internal cues, the body learns to anticipate and counteract some physiological effects of drugs.

One central tenet of Alcoholics Anonymous is: "We are without defense against the first drink." That is to say, consuming even a small amount of alcohol can easily lead to a full-blown relapse.

But why does consuming a small amount of a drug cause alcohol-experienced individuals to crave more? Shouldn't feeding a craving--even a little--cause it to lessen?

A new study published in the APA journal Experimental and Clinical Psychopharmacology (Vol. 12, No. 2) suggests that the rush of craving may occur at least in part because the body can learn to anticipate and compensate for a drug's effects--a mechanism that also accounts for the often-observed phenomenon of drug tolerance.

As a consequence, a small amount of alcohol can trigger the body to prepare for a large amount, and when that large amount does not come, withdrawal symptoms such as nausea and fever occur, says one of the study's authors, Shepard Siegel, PhD, a psychology professor at McMaster University in Canada.

"This study indicates that early internal effects can act as drug onset cues," explains Siegel, who co-authored the paper with Robert V. McDonald, PhD, an assistant psychology professor at Wilfrid Laurier University in Canada.

In most previous research, only external cues, such as the color or smells associated with a drug-administration environment, had been found to trigger the body's anticipatory response.

That response, explains Siegel, consists of preparations to return bodily functions, such as temperature, back to baseline levels after being affected by the drug.

## External signals

Like the dogs in Ivan Pavlov's classic conditioning experiments (see page 20), drug addicts learn to associate environmental cues with upcoming events. A morphine addict's body may become more sensitive to pain

when external cues--perhaps the playing of a particular record instead of the bell Pavlov's dogs heard--often precede administration of the drug, and its pain-relieving effects.

Drug addicts tend to use drugs in a particular setting, says Barbara Ramos, PhD, a colleague of Siegel's and research associate at McMaster University. "Anything from outside the organism--light, sound, taste, and place--can serve as an extroceptive cue," she explains. For example, a heroin addict might always shoot up in a bathroom with the shower running, and the characteristic sights and sounds of this location will be associated with the coming administration of the drug.

"These cues indicate [the drug user's] body should be prepared to counteract the drug," says Ramos. And the body responds by doing just that, which is why experienced drug users--those who frequently pair an environment with drug administration--can tolerate more than novice drug users, she says.

However, learned tolerance only works when drugs are taken in the same environment as usual, notes Ramos.

One study, published in Pharmacology and Behavior (Vol. 37, No. 1) by Christine L. Melchior, PhD, a psychologist at the National Institutes of Health, demonstrates this point dramatically.

Melchior's experiment on drug tolerance in mice involved two conditions. In both conditions the mice were injected with an amount of ethanol equal to 3.5 grams per kilogram of the animal's weight. After four consecutive days of this procedure, researchers placed half of the mice in a different environment than the one in which they were usually dosed; the other half stayed in their usual spots. The experimenters then injected all the mice with 5.5 grams per kilogram--a usually fatal amount--and not one of the mice dosed in the familiar environment died. However, 60 percent of the rats injected in new environments died.

"Obviously the context of getting the injections is something they were picking up and responding to," says Melchior, explaining that this allowed the mice to anticipate, compensate for and better tolerate the drug.

Internal cues

New research by Siegel, one of the first to observe the body's compensatory response to external cues, suggests that internal events may also trigger such reactions.

In the Experimental and Clinical Psychopharmacology study, experimenters injected 35 rats with 50 milligrams per kilogram of morphine every day for 10 days. On the 11th day, rats received only 5 milligrams per kilogram of the drug. Usually, a morphine injection causes an animal's temperature to rise, but when these morphine-experienced rats received a lower-than-usual dose, their temperatures dropped.

Siegel hypothesizes that the rats' bodies sought to compensate for expected drug effects by dropping in temperature. But that response turned out to be overkill when the usual large dose of morphine did not follow the initial small injection.

Hypothermia, says Siegel, is a typical morphine withdrawal symptom, and in rats so are behaviors such as "wet-dog shakes" and genital licks. All of these reactions occurred in the rats' responses to small doses because the rats' bodies anticipated and had already begun compensating for the expected larger dose.

"This new research has shown that, depending on how a drug is administered, it takes a long time for it to reach its full effect on the body," says Ramos. The drug's early effects--perhaps a slight temperature rise or sluggishness--can serve as internal cues that trigger a drug-experienced animal's compensatory response, she explains.

Potential applications

As mentioned earlier, a taste of alcohol can cause alcoholics to feel withdrawal symptoms when their bodies expect, but do not receive, the effect of a large amount of the drug. The discomfort and other symptoms associated with a compensatory response can cause the addict to crave more alcohol, which, if ingested, restores the body to homeostasis. In other words, alcoholics are without defense against the first drink.

However, says Siegel, they don't have to be. If the body learns to expect alcohol, it can also be taught not to, he explains. For example, a treatment program might have former addicts take a small dose of a drug, and then wait out the subsequent withdrawal symptoms. If this is done often enough, the compensatory response to environmental cues grows weaker.

"Past attempts at cue-exposure therapy has not been terribly successful," notes Siegel. But, he says, perhaps if these internal cues could be broken as well, drug addicts would have more of a defense against physical responses that urge them to use.