Drug-Induced Suppression of Conditioned Stimulus Intake: Reward, Aversion, and Addiction

For the month of January, we are highlighting Chapter 5 of Reilly and Schachtman’s “Conditioned Taste Aversion: Behavioral and Neural Processes”. This chapter by Grigson, Twining, Freet, Wheeler and Geddes is entitled “Drug-induced suppression of conditioned stimulus intake: Reward, aversion, and addiction”.

One of the surprising findings of conditioned taste aversion (CTA) research is the ability of drugs of abuse to support CTA learning. First reported in the early 1970s, this ability to induce taste aversions has been reported for every drug of abuse that has been investigated. Several attempts have been made to resolve this apparent “paradox”; however, none has proved successful. The present chapter by Grigson and her colleagues is a review of the recent attempt to reexamine this paradox in the light of the reward comparison hypothesis.

In the beginning of the chapter, the authors discuss the nature of addiction and two of its defining characteristics, namely, chronic relapse and devaluation of natural rewards. The authors also note that while there are several models for the study of craving and relapse, there is no animal model for the study of drug-induced devaluation of natural rewards. According to Grigson and her colleagues, drug-induced CTA provides such a model.

The reward comparison hypothesis, primarily developed by Grigson, is derived from the anticipatory contrast effect that shows that rats avoid consumption of saccharin when paired with a highly preferred sucrose solution. In other words, rats reduce saccharin intake in anticipation of the more rewarding and preferred sucrose. Likewise, argued Grigson, rats avoid consumption of the taste paired with a drug of abuse because the value of the taste cue pales in comparison with the more rewarding and preferred drug reward anticipated in the near future. It is therefore the well-documented rewarding effects of drugs of abuse and not their hypothetical aversive effects that mediate drug-induced suppression of taste stimuli. As such, drug-induced CTA may serve as a model for the study of drug-induced devaluation of natural rewards.

Grigson and her colleagues reinterpreted the CTA literature to argue that drug-induced CTA data have been largely misinterpreted as a classical CTA, wherein a treatment (either pharmacological, e.g., LiCl, or non-pharmacological, e.g., radiation) produces conditioned suppression of taste stimulus because of the known illness-producing effects of the treatment. As summarized in the chapter, this may be an unlikely explanation with drugs of abuse for a number of reasons. First, unlike classical toxins, drugs of abuse are readily self-administered by humans and other animals and produce conditioned place preferences. Furthermore, while toxins suppress both instrumental and consummatory behavior, drugs of abuse increase instrumental behavior and suppress
consummatory behavior. Finally, drugs of abuse do not elicit active rejection responses in the taste reactivity tests, whereas classical toxins do. On the other hand, drug-induced suppression is analogous to the anticipatory contrast, such that both preparations use a rewarding US that results in the avoidance of the taste CS.

Next the authors discuss the supporting evidence for the reward comparison hypothesis that comes from a number of studies that examined the nature the CS, deprivation state of the subject animal, selectively bred strains (such as Lewis and Fischer strains), drug preexposure and neuroanatomical studies that used lesions to dissociate conditioned suppression induced by toxins from that induced by drugs of abuse.

First, the suppressive effects of sucrose (i.e., anticipatory contrast) and drugs of abuse (i.e., reward comparison) are dependent on the nature of the gustatory CS. Thus, rats avoid consumption of rewarding saccharin when paired with either cocaine or morphine but fail to do so when neutral NaCl serves as CS. LiCl, on the other hand, suppresses consumption of both taste stimuli.

Second, the suppressive effects of sucrose and drugs of abuse, but not LiCl, are affected by the deprivation state of the animal. Thus, both food and water deprivation reduce the suppressive effects of morphine, cocaine and sucrose, but fail to do so when LiCl is used as US.

Third, the suppressive effects of sucrose and cocaine, but not LiCl, are greater in drug-sensitive Lewis rats than less-sensitive Fischer rats. If, according to the reward comparison hypothesis, rewarding effects mediate suppression of CS consumption, the magnitude of cocaine-induced suppression should be greater in Lewis rats than Fischer rats, and this is indeed what the authors report.

Fourth, a history of chronic morphine treatment in Sprague-Dawley rats that induces neurochemical changes characteristic of drug-sensitive Lewis rats exaggerates the suppressive effects of sucrose and cocaine but not LiCl.

Finally, lesions of gustatory thalamus disrupt the suppressive effects of both sucrose and morphine, but not LiCl. Moreover, lesions of gustatory cortex disrupt morphine-induced suppression but not LiCl-induced suppression. The authors note, however, that these lesions do not produce these disruptive effects with high doses of cocaine.

The authors’ argument for the reward comparison hypothesis is in essence an argument by analogy, such that the drug-induced suppression is similar to the suppression induced by rewarding sucrose (i.e., anticipatory contrast effect) but unlike the suppression induced by classical toxins (i.e., conditioned taste aversion). Therefore, if drug-induced avoidance of the taste cue is mediated by the drug’s rewarding effects, the suppression of CS intake should be related to
some measure of the rewarding effects of the drug. In an attempt to test this prediction, Grigson and her colleagues allowed rats to consume saccharin and to self-administer cocaine at the same time. In support of the reward comparison hypothesis, individual differences in saccharin avoidance predicted the propensity to self-administer cocaine, such that animals that showed strong suppression of saccharin CS (large suppressers) were more likely to self-administer cocaine.

Reward comparison is an attempt to resolve the apparent paradox wherein drugs of abuse induce CTA. According to Grigson and her colleagues, the drug-induced CTA literature has been misinterpreted as a classical CTA and is best understood in the light of the reward comparison hypothesis that argues that drugs of abuse suppress consumption of taste CS because the value of the taste is less than that of the more rewarding drug. The authors argue that this may serve as a first model for the drug-induced devaluation of natural rewards. However, while the authors provide several lines of evidence in favor for the hypothesis, it is important to note that the present hypothesis rests on the assumption that “the value of the taste cue pales in anticipation of the highly rewarding properties of the drug” (p. 76). Whether this is so has been a subject of a number of studies and review papers and the data so far suggest that this might not be the case. For example, when offered a choice between cocaine and saccharin (at comparable doses and concentrations used in CTA research), the large majority of rats readily take saccharin to the exclusion of cocaine (Lenoir et al., 2007; Cantin et al., 2009; Ahmed, 2010). This is an important finding that should be taken into consideration in an attempt to resolve the paradox of CTA research. As such, drug-induced conditioned taste aversions remain to be an interesting and important finding for drug abuse research (i.e., the possibility that drugs of abuse have multiple properties, not all of which are rewarding, positive reinforcing), and for which the mechanism is yet to be explained.