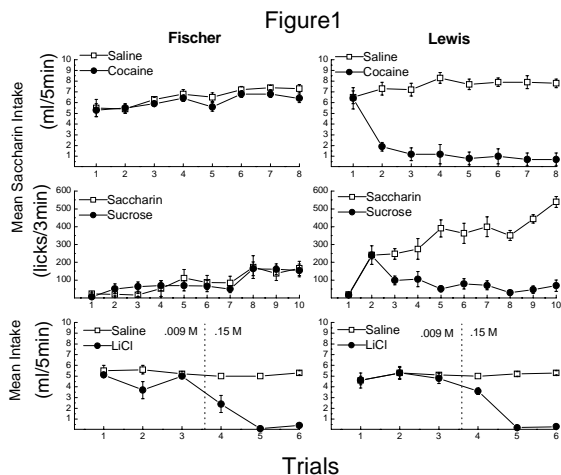


*The classical notion of taste aversion learning originated with radiation sickness as documented in the classical work of John Garcia and his colleagues (see highlight by Garcia). In Garcia's original work with radiation, he argued that the aversive consequences of radiation poisoning were associated with concurrently available foods, and this association resulted in an aversion to these foods and their subsequent avoidance. Such conditioned aversions were soon reported to be induced by a variety of compounds, including, albeit paradoxically, compounds generally assumed to be non-toxic in nature and, in fact, reinforcing. As Dr. Grigson notes in her highlight, these extensions to drugs of abuse generated considerable theoretical discussion, but it wasn't until Dr. Grigson's 1997 article in Behavioral Neuroscience that the avoidance of tastes associated with drugs of abuse was examined in the context of their rewarding effects (as opposed to the traditional toxicological framework in which aversion learning originated). In her highlight, Dr. Grigson describes the background for her work, the data supporting her position and the implications of this reconceptualization (for the fields of taste avoidance and of drug abuse).*

**See Below**

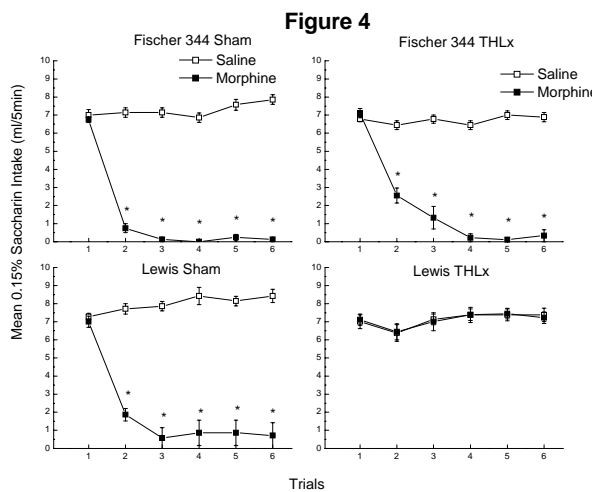
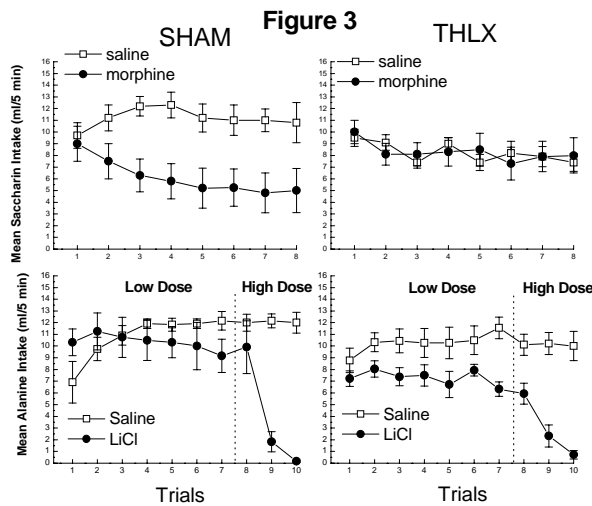
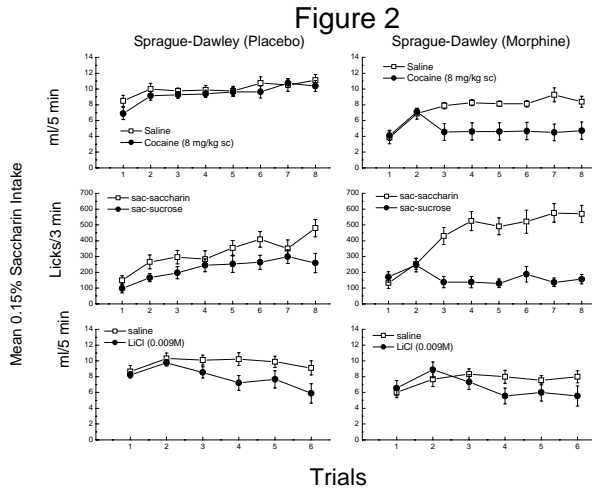
**Conditioned taste aversions and drugs of abuse: The paradox.** A conditioned taste aversion (CTA) occurs when rats avoid intake of a gustatory conditioned stimulus (CS) after it has been paired with an aversive, illness-inducing agent such as lithium chloride (LiCl) or x-radiation<sup>1,2</sup>. Not long after CTAs were discovered with emetic agents as the unconditioned stimuli (US), Le Magnen<sup>3</sup> reported that rats also avoid intake of a gustatory CS when paired with a drug of abuse. By 1970, this group concluded that, like LiCl and x-radiation, drugs of abuse also support CTA learning<sup>4</sup>. Here began the paradox whereby highly rewarding drugs of abuse, drugs that rats and man would self-administer, also were thought to have aversive properties. Strong support for this hypothesis was provided when several laboratories found that the increase in operant responding for the drug was accompanied by a simultaneous avoidance of the taste cue that predicted its availability<sup>5-7</sup>. A number of review articles followed suggesting that stimulus novelty, drug shyness, or fear, for example, may mediate the conditioned aversion<sup>8-10</sup>.

**Anticipatory contrast.** About a decade after drugs of abuse were found to support CTA learning, the late Charles Flaherty reported that rats also avoided intake of a saccharin CS when paired with access to a highly palatable sucrose reward<sup>11</sup>. This phenomenon was referred to as an *anticipatory contrast* effect because reduced intake of the taste cue was thought to reflect an associative process whereby the perceived value of the saccharin CS paled in anticipation of the availability of the preferred sucrose reward<sup>12,13</sup>. As a graduate student in Charlie's laboratory, I studied the fundamental aspects of this phenomenon for several years. As a postdoctoral fellow, I was beginning to study conditioned taste aversion learning with emetic agents and happened to listen to Linda Parker describe how rats gaped following the presentation of a taste cue paired with the aversive agent, LiCl<sup>14,15</sup>, but not when paired with drugs of abuse<sup>16,17</sup>. Finally, it came clear. If one were to view drugs of abuse as rewarding, then the resultant reduction in CS intake is simply another form of anticipatory contrast. Over the next decade, we tested the merits of this new hypothesis.



**The Reward Comparison Hypothesis.** The Reward Comparison hypothesis states that rats avoid intake of a taste cue when paired with a drug of abuse because the value of the taste cue pales in anticipation of the highly rewarding properties of the drug. We reasoned that if this hypothesis was correct, then drug-induced suppression of CS intake should be affected by factors that affect anticipatory

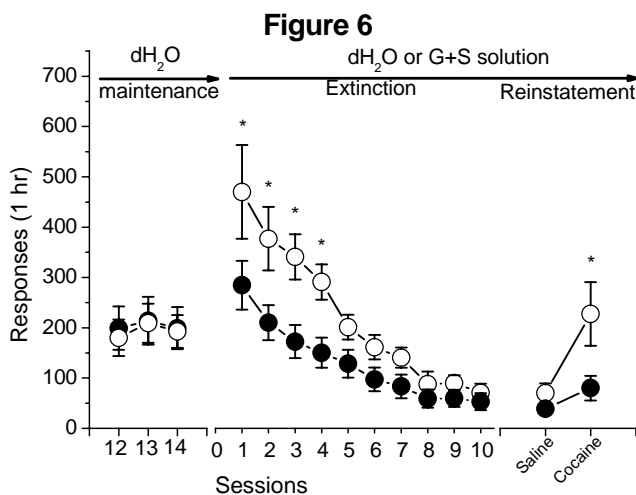
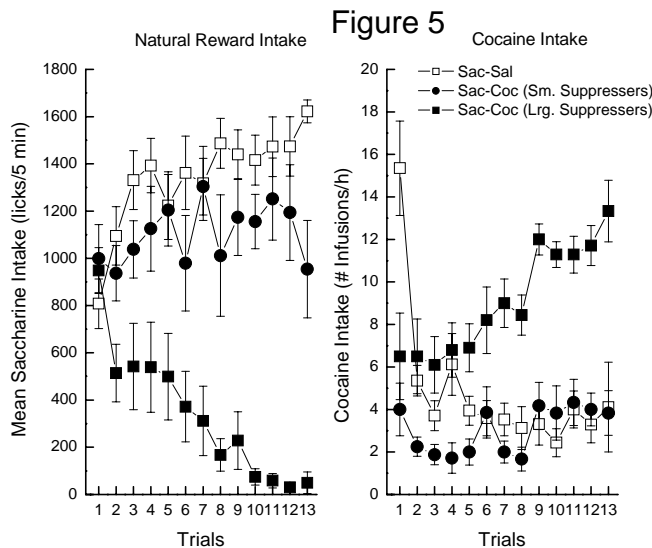
contrast, but not by factors that affect a LiCl-induced CTA.



**Evidence in support of the reward comparison hypothesis. (a)** In our first paper, we demonstrated that, like the suppressive effects of sucrose<sup>18</sup>, the suppressive effects of morphine and cocaine, but not LiCl, depend upon the nature (e.g., saccharin vs. salt) of the gustatory CS<sup>19,20</sup>. **(b)** We also showed that the suppressive effects of sucrose and morphine, but not LiCl, increase with increasing concentrations (i.e., value) of the saccharin CS<sup>18,19,21</sup>. **(c)** Later papers showed that the suppressive effects of sucrose and drugs of abuse, but to a lesser extent LiCl, are reduced when the rats are tested in a food- or water-deprived state<sup>22-24</sup>. **(d)** The suppressive effects of cocaine and sucrose, but not LiCl, were found to be greater in reward sensitive Lewis, than less sensitive Fischer 344, rats (see Figure 1)<sup>25</sup>. This finding was consistent with an earlier report on cocaine<sup>26</sup>, though opposite to the pattern reported for morphine<sup>27</sup>. Recent data, however, may provide an explanation as Fischer rats are more sensitive to the aversive kappa receptor-mediated properties of opiates<sup>28</sup>. **(e)** Chronic morphine treatment augmented the suppressive effects of weak cocaine and sucrose, but not weak LiCl, in Sprague-Dawley rats (see Figure 2)<sup>29</sup>. **(f)** Lesions of the gustatory thalamus also

dissociate the phenomena by preventing the suppressive effects of sucrose and morphine, but not LiCl CTAs in Sprague-Dawley rats (see Figure 3)<sup>30-32</sup>. **(g)** Finally, consistent with the conclusion that morphine is rewarding in Lewis rats, but aversive in Fischer rats, lesions of the gustatory thalamus failed to disrupt the suppressive effects of morphine in Fischer rats, while fully eliminating the effect in Lewis rats (see Figure 4)<sup>33</sup>. Thus, while drugs of abuse have aversive properties<sup>34-36</sup>, the evidence supports the hypothesis that rats suppress intake of a saccharin cue following taste-drug pairings because they are anticipating the availability of well-known rewarding drug properties. If this hypothesis proves correct, it is the first rodent model for the systematic study of drug-induced devaluation of natural rewards – a condition that plagues the life of the addict, his or her family, and society as a whole<sup>37-39</sup>.

**Beyond the reward comparison hypothesis: Drug-seeking and relapse.** In the process of testing the reward comparison hypothesis, we have made a number of new discoveries that have greatly expanded the model and our



understanding of the problem. First, whether the drug is administered passively<sup>40</sup>, or actively (i.e., self-administered)<sup>41</sup>, some Sprague-Dawley rats are more likely to avoid intake of the taste cue than are others (see Figure 5, left panel). These rats are referred to as large suppressors. Greater avoidance of the taste cue is associated with a greater cue-induced elevation in circulating corticosterone<sup>40</sup>, greater cocaine self-administration (see Figure 5, right panel)<sup>41</sup>, and greater cocaine-seeking following an extended period of abstinence<sup>41</sup>. Thus, the model is not only sensitive to individual differences in drug-induced devaluation, but to cue-induced craving, drug-seeking, and relapse as well.

**Reward comparison: Cross-modal and bi-directional.** As shown, drugs of abuse can devalue natural rewards. Natural

rewards, in turn, also devalue drugs of abuse in rats, monkeys, and man<sup>42-46</sup>. Indeed, we have recently found that just 5 min daily access to a highly palatable sweet is sufficient to disrupt acquisition of cocaine self-administration<sup>47</sup> and to fully block drug-induced reinstatement (see Figure 6)<sup>48</sup>. Reward comparison, then, is bi-directional. It is the addict's Achilles' heel and it is, at the same time, his or her hope for recovery.

**Drug of abuse: Rewarding or Aversive?** Taken together, our data are consistent with the conclusion that rats avoid intake of a taste cue when paired with a drug of abuse because the perceived value of the taste cue pales in comparison with the highly rewarding properties of the drug. There is, however, some evidence for a role for aversive properties. For example, the disruptive effect of thalamic lesions can be overridden by the use of a high dose of cocaine. Moreover, we find that rats gape when a taste cue that has been paired with this high dose of cocaine is infused directly into the oral cavity (Twining et al., Society for Neuroscience, 2005). Is this evidence for a conditioned taste aversion? Decidedly. Is it a CTA as we know it? Not likely. Rather, we are hypothesizing that the conditioned taste aversion, in this case, reflects cue-induced withdrawal, which is known to be aversive and which supports aversive taste reactivity behaviors<sup>49</sup>. Thus, just as a drink is an effective antidote for withdrawal in the alcoholic, these gapes were eliminated when the rats were pretreated with a single iv dose of cocaine prior to CS infusion. Rats, then, respond to the rewarding properties of drugs. With repeated experience, however, dependence/addiction can develop, and with it, the associated aversive states. These states, too, are potentially conditionable. The conditioned reduction in CS intake, then, cannot be taken as evidence for aversion or reward. If multiple measures are used, however, it is possible to use this paradigm to track the contribution of reward and aversion to the complex transition from use to abuse, addiction, withdrawal, and relapse.

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