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The State of the Reward Comparison Hypothesis: Theoretical Comment on Huang and Hsiao (2008)

Patricia Sue Grigson
Department of Neural and Behavioral Sciences, Pennsylvania State University College of Medicine

Abstract

Rats avoid intake of a gustatory cue following pairings with a drug of abuse, such as morphine or cocaine. Despite the well-established rewarding properties of these drugs, the reduction in intake of the taste cue has been interpreted as a conditioned taste aversion for decades. In 1997, I proposed the reward comparison hypothesis suggesting that rats avoided intake of the drug-associated taste cue because the value of the taste cue pales in comparison to the highly rewarding drug of abuse expected in the near future. In this issue of *Behavioral Neuroscience,* A.C.W. Huang and S. Hsiao (2008) challenge the reward comparison hypothesis by showing parallels between amphetamine and LiCl-induced suppression of CS intake. This commentary addresses the current state of the reward comparison hypothesis in the context of the experiments completed by Huang and Hsiao and their new task-dependent drug effects hypothesis.

Keywords

anticipatory contrast; sucrose; cocaine; withdrawal; self-administration

A conditioned taste aversion (CTA) occurs when rats avoid intake of a gustatory conditioned stimulus (CS) after it has been paired with an illness-inducing agent such as lithium chloride (LiCl) or x-radiation (Garcia, Kimmeldorf, & Koelling, 1955; Nachman & Ashe, 1973; Smith, Morris, & Hendricks, 1964). These CTAs occur with all gustatory CSs tested, so long as the tastant is salient and, preferably, novel (Kalat, 1974; Kalat & Rozen, 1970). The aversion induced by these illness-inducing agents is most readily associated with a gustatory CS and the conditioned aversion to these gustatory stimuli can occur despite the use of very long interstimulus intervals. As such, the discovery of this new phenomenon created considerable controversy as it challenged at least two fundamental principles of animal learning theory—equipotentiality (all CSs are equal) and contiguity (the US must follow the CS closely in time). For a discussion see Garcia et al. (Garcia, Hankins, & Rusiniak, 1974).

It was in this context that scientists discovered that not only traditional emetic agents, but also drugs of abuse suppress intake of an associated gustatory CS (Le Magnen, 1969). Not surprisingly, this reduction in CS intake was interpreted as a CTA (Lester, Nachman, & Le Magnen, 1970). With further study, the phenomenon was found to occur with all drugs of abuse tested (Cappell & LeBlanc, 1971; Cappell, LeBlanc, & Endrenyi, 1973; Castane, Soria, Ledent, Maldonado, & Valverde, 2006; Glowa, Shaw, & Riley, 1994; Grigson, Twining, & Carelli, 2000; Miller, Kelly, Neisewander, McCoy, & Bardo, 1990; Sherman,

Correspondence concerning this article should be addressed to: Patricia Sue Grigson, Department of Neural and Behavioral Sciences, Pennsylvania State University College of Medicine, 500 University Drive, Hershey, PA 17033, psg6@psu.edu.

Pickman, Rice, Liebeskind, & Holman, 1980; Vogel & Nathan, 1975) across a range of doses (Parker, 1991) and when administered intraperitoneally (ip), subcutaneously (sc), intravenously (iv), or, in some cases, even when administered directly into the nucleus accumbens (Bechara & van der Kooy, 1985; Cappell & LeBlanc, 1971; Mucha & Herz, 1986; Shoaib & Stolerman, 1995; Wise, Yokel, & DeWit, 1976). Finally, the "paradoxical" nature of this finding was not overlooked, as scientists struggled to understand how and why highly rewarding drugs of abuse, drugs that were readily self-administered by rats and man (van Ree, 1979), also supported conditioned taste aversion learning (Goudie, 1979; Hunt & Amit, 1987; Parker, 2003; Stolerman & D'Mello, 1981).

A little more than a decade after drugs of abuse were found to support CTA learning, the late Charles Flaherty reported that rats also avoid intake of a saccharin CS when paired, in once daily sessions, with a highly preferred 32% sucrose solution (Flaherty & Checke, 1982). 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 highly preferred sucrose reward. Indeed, in a within subjects design, it was shown that the reduction in intake of the taste cue depended upon the value of the anticipated 32% sucrose reward, not upon the memory of a 32% sucrose solution received 24 h earlier (Flaherty & Rowan, 1985). Anticipatory contrast effects, then, are thought to depend upon the development of a Pavlovian associative relationship between the saccharin CS and the sucrose US (Flaherty & Grigson, 1988). The lesser reward CS is avoided in anticipation of the imminent availability of the preferred US reward (Flaherty, 1996; Flaherty & Grigson, 1988).

Given this finding, in 1997, I reinterpreted published data showing that rats avoid intake of a taste cue when paired with a drug of abuse. Specifically, I hypothesized that, if one were to view drugs of abuse as rewarding, then the ensuing reduction in CS intake is simply another form of anticipatory contrast (Grigson, 1997). Thus, rats avoid intake of a drug-associated taste cue because the value of the taste cue pales in comparison to the powerful drug reward that is anticipated in the very near future.

In this issue of *Behavioral Neuroscience,* Huang and Hsiao (2008) argue against this hypothesis and pose a theory they refer to as the "task-dependent drug effects hypothesis." Echoing Wise (Wise et al., 1976), this alternative hypothesis suggests that drugs are compound stimuli with both positive and negative effects. Moreover, in keeping with early studies by Garcia and colleagues (Garcia, McGowen, Ervin, & Koelling, 1968), Huang and Hsiao suggest that the aversive effects of the drugs (including visceral responses) are associated with the gustatory cue and the rewarding effects (involving activation of central dopaminergic pathways) are associated with environmental cues. As a result, rats can show a CTA to the taste cue and a conditioned preference for the drug-associated context at the same time in the same experiment (Reicher & Holman, 1977). The following text will address the experiments completed by Huang and Hsiao (2008) and the arguments developed in the General Discussion in support of their task-dependent drug effects hypothesis versus the reward comparison hypothesis.

In the paper where the reward comparison hypothesis was first proposed (Grigson, 1997), one experiment demonstrated that the suppressive effects of matched doses of morphine and cocaine but not LiCl were greater when a sweet 0.15% saccharin solution, rather than a "neutral" 0.1 M NaCl solution, served as the gustatory CS. In addition, as with anticipatory contrast (i.e., sucrose-induced suppression of CS intake; Flaherty, Turovsky, & Krauss, 1994), the magnitude of the suppressive effects of a 15 mg/kg dose of morphine on CS intake increased as the concentration ("palatability") of the saccharin CS increased from 0.015% to 0.075% to 0.15%.

Huang and Hsiao addressed these observations in their first experiment by testing whether d-amphetamine, but not LiCl-induced suppression of CS intake would increase as the "palatability" of the saccharin cue increased. Specifically, they used a 2.0 and 4.0 mg/kg dose of d-amphetamine US; a 4 and 8 ml/kg dose of 0.15 M LiCl US; and 0.015%, 0.075%, or 0.15% saccharin as the gustatory CS. Except for a few slight procedural differences, the study was conducted much like those described (Grigson, 1997). There were five CS-US pairings, followed by one CS only test. The data were converted into a suppression ratio relative to first trial intake, but, unfortunately, the data from the first trial were omitted from the analyses and from the figures (see Figures 1 and 2; Huang & Hsiao, 2008). In addition, the three-way saccharin concentration × dose × trials interaction was significant for the amphetamine study, but post hoc tests were not conducted. This 3-way interaction did not attain statistical significance in the LiCl experiment. Even so, observation of the data in their Figures 1 and 2 seems to indicate that, while the suppressive effects of the lower doses of the drugs did not differ as a function of CS concentration, the suppressive effects of the higher doses of both amphetamine and LiCl did increase with increasing concentrations of the saccharin CS. These data align the amphetamine and the LiCl data, but, as the authors point out, ultimately provide inconclusive evidence against the reward comparison hypothesis because the suppressive effects of sweets, drugs, and LiCl can increase as a function of the palatability and/or concentration of the saccharin CS (Ellins & Kennedy, 1995; Flaherty et al., 1994; Garcia et al., 1974; Grigson, 1997).

In their second experiment, Huang and Hsiao posed an interesting hypothesis: If rats avoid intake of a taste cue following taste-drug pairings because they are *anticipating* the availability of a preferred drug of abuse, as suggested by the reward comparison hypothesis, then suppression of CS intake should not occur if the injection of the amphetamine US were to precede access to the saccharin CS in a backward conditioning procedure. If, on the other hand, amphetamine works like LiCl, then suppression of CS intake (i.e., a CTA) should occur following forward or backward conditioning (Franchina & Dietz, 1981; Yamamoto, Shimura, Sako, Yasoshima, & Sakai, 1994; but see Spector, Breslin, & Grill, 1988). In fact, CS intake was reduced following a single backward pairing with either a 2 mg/kg dose of amphetamine or a 4 ml/kg dose of 0.15 M LiCl. A 20 to 30 min interstimulus interval was used in this study. These data, which parallel an earlier finding with a 1.43 mg/kg dose of amphetamine (Reicher & Holman, 1977), were taken as evidence against the reward comparison hypothesis.

Although this conclusion seems reasonable, there are alternative interpretations of the data that deserve consideration. First, as suggested by Huang and Hsiao, the suppression of CS intake following backward conditioning with amphetamine may, like that induced by LiCl, be evidence of CTA learning. Second, unlike other abused substances, amphetamine has marked appetite suppressant effects (Caul, Jones, & Barrett, 1988) that are readily conditionable (Poulos, Wilkinson, & Cappell, 1981). Thus, the reduction in intake of the saccharin cue following the backward amphetamine-saccharin pairing could be due to conditioned anorexia. Finally, although anticipatory contrast requires, by definition, that the taste cue precede presentation of the US, contrast effects occur in an anterograde and a retrograde fashion (Flaherty, 1996). Thus, rats will also reduce intake of a lesser preferred taste cue when compared with either the short- or the long-term memory of a more preferred reward (e.g., in simultaneous or successive negative contrast, respectively). As such, in the Huang and Hsiao paradigm, rats could have avoided intake of the saccharin cue following the prior amphetamine-saccharin pairing via a successive negative contrast mechanism, for example, because the value of the saccharin cue at test paled in comparison with the memory of the value of the amphetamine received 48 h earlier. In support of this possibility, Capaldi, Sheffer, and Pulley (1989) reported that rats consumed less 0.15% saccharin than saccharin-saccharin controls if they received access to a preferred 32% sucrose solution

randomly, either 90 min before or 90 min after access to the saccharin cue. These data suggest that contrast effects also may develop with backward conditioning and, in this case, with quite a long interstimulus interval. This leaves open the possibility that the reduction in CS intake obtained following backward conditioning with amphetamine also could be mediated by a contrast mechanism.

In the final experiment, Huang and Hsiao hypothesized that, if amphetamine-induced suppression of CS intake was due to a reward comparison mechanism, then amphetamine should offset (or reduce) the CS suppression induced by a putatively aversive agent, LiCl, when the two USs are combined in an "additivity" study. If, on the other hand, a CTA mediates the suppressive effects of amphetamine, then they reasoned that the suppressive effects of amphetamine and LiCl should be additive. The results of this third experiment failed to show either additivity or attenuation with the combined injection of a 2 mg/kg dose of amphetamine and a 4 ml/kg dose of 0.15 M LiCl. This finding is consistent with a recent report that failed to find evidence for additivity between ethanol- and cocaine-induced suppression of CS intake in male Sprague-Dawley rats (Busse, Verendeev, Jones, & Riley, 2005), but differs from earlier reports that did find evidence of such additive effects in female Long-Evans rats (Etkind, Fantegrossi, & Riley, 1998; Grakalic & Riley, 2002). The failure to find additive effects in the present study may have been due to floor effects. Even so, because LiCl and amphetamine "appeared to have a synergistic effect on intake suppression," Huang and Hsiao took these data as evidence against the reward comparison hypothesis and in favor of the CTA account.

Nevertheless, this study too, fails to provide convincing evidence against the reward comparison hypothesis. First, as described, statistical analysis of the data did not find evidence for either additivity or attenuation with the combined injection of the two drugs. Second, the study was based on the assumption that a reduction in CS intake mediated by reward comparison (or contrast) would antagonize a reduction in CS intake mediated by LiCl. In fact, to this author's knowledge, an additivity study has not been conducted between a sucrose-paired CS and a LiCl-paired CS. We have, however, conducted a study in male Sprague–Dawley rats to test for potential additive effects of a sucrose-paired CS and a morphine-paired CS. If morphine, like amphetamine, has aversive properties, as suggested by Huang and Hsiao, then sucrose contrast should offset (or attenuate) the suppressive effects of morphine on CS intake. Yet, this is not what we found. Thirty-two rats were food-deprived to 80% of their free-feeding body weight. They were placed in our standard test chambers (Med Associates Inc, St. Albans, VT) and given 3 min access to a 0.15% saccharin solution. Then, two minutes into a 5-min interstimulus interval, half of the rats were injected ip with saline (n = 16) and half were injected ip with a low, 5 mg/kg dose of morphine (n = 16). The rats were returned to the chambers. Three minutes later, half of the rats from each drug condition (n = 8/cell) were given 3 min access to either the same saccharin solution or to a weak 0.3 M sucrose solution. The number of licks made for saccharin and sucrose were measured using a contact relay. This regimen continued for 14 days, with no evidence of additivity or attenuation. Thereafter, the dose of morphine was increased from 5 to 10 mg/kg and the concentration of sucrose was increased from 0.3 to 0.6 M for three additional trials. Again, we found no evidence of additivity or attenuation in the saccharin-morphine + sucrose group versus the saccharin-morphine + saccharin group or the saccharin-saline + sucrose group. Finally, because other studies indicated that contrast effects can be masked by the need for food or fluid, the rats were returned to a nondeprived state and tested a week later across two additional trials. The higher 10 mg/kg dose of morphine and 0.6 M concentration of sucrose continued to serve as the USs. The results of this test revealed clear additivity. The data, averaged across the two nondeprived test days, are shown in Figure 1.

The results of a one-way analysis of variance showed that intake of the saccharin CS varied as a function of treatment group, $F(3, 28) = 11.59$, $p < .0001$. Post hoc Newman–Keuls tests found that, while neither the sucrose nor the morphine US suppressed intake of the saccharin cue when presented separately, ps > .05, intake of the saccharin cue was significantly reduced compared with intake by the saccharin-saline + saccharin controls when the two morphine and sucrose USs were presented in combination, $p < .05$. Several additional studies are needed to fully address this issue of additivity but, the very least, these results show that the suppressive effects of a sweet can be additive with those of a drug of abuse and the suppressive effects of a drug of abuse can (Etkind et al., 1998; Grakalic & Riley, 2002), in some circumstances, be additive with those of an aversive agent. Thus, we must test Huang and Hsiao's basic assumption that the suppressive effects of a sweet will reduce, rather than augment, the suppressive effects of an aversive agent, like LiCl.

In addition to their three experiments, Huang and Hsiao (2008) also bring up other issues in their General Discussion. They argue that not only the suppressive effects of sweets and drugs of abuse, but also those of LiCl, are reduced by the use of a palatable sucrose CS in food-deprived rats. As we reported (Gomez & Grigson, 1999), this is true, but relative to the suppressive effects of sweets and drugs, the suppressive effects of LiCl are far more impervious to the use of a palatable cue or to the need for food or fluid (Gomez & Grigson, 1999; Grigson, Lyuboslavsky, Tanase, & Wheeler, 1999; Grigson, Twining, Freet, Wheeler, & Geddes, 2008; Twining et al., 2008).

As described, earlier studies showed that a morphine or a cocaine US exerted greater suppression of intake of a saccharin than an NaCl CS (Grigson, 1997). Thus, like conventional sucrose-induced suppression of CS intake (Flaherty et al., 1994), a more palatable fluid also supports greater drug-induced suppression. Huang and Hsiao (2008) note that Sorge, Fudge, and Parker (2002) argued against the reward comparison hypothesis by demonstrating that rats failed to show morphine-induced suppression of intake of a salt CS even when the salt cue became highly preferred following treatment with the diuretic, furosemide. As we argue elsewhere (Grigson et al., 2008), the dose of furosemide used by Sorge et al. was 20 times that required to elicit a sodium appetite (Lundy, Blair, Horvath, & Norgren, 2003). As such, the value of salt in this study may have rivaled the morphine reward. In the anticipatory contrast paradigm, a contrast effect actually reverses to a reinforcement effect (i.e., results in an increase in CS intake) when the value of the CS begins to approach that of the US (Flaherty, Grigson, Checke, & Hnat, 1991; Flaherty & Rowan, 1986). It is interesting to note that Sorge et al. (2002) reported the development of a conditioned flavor preference, rather than a conditioned suppression of CS intake, following treatment with furosemide. The same dose of furosemide, in comparison, had no effect on the expression of the LiCl-induced CTA. This is important because it dissociates the phenomena and because this dose of furosemide could, itself, have been toxic (Lundy, Calviero, Bradley, Liang, & Norgren, 2004). In sum, contrast effects increase with increasing concentrations of a saccharin cue but can reverse to a reinforcement effect as the CS closely approaches the value of the US. In addition, it should be noted that suppression of CS intake also has been obtained with both drugs of abuse and with sucrose when an aversive solution, such as malic acid, serves as the CS. For a discussion, see Grigson et al. (2008). Rats, then, readily compare not only good with better, but bad with better as well.

Another data set addressed by Huang and Hsiao involves the use of the selectively bred strains: Lewis and Fischer 344 rats. As described in our earlier papers and in a recent review (Grigson, 2000; Grigson & Freet, 2000; Grigson et al., 2008), Lewis rats are generally viewed as more reward sensitive than Fischer rats (Ambrosio, Goldberg, & Elmer, 1995; George & Goldberg, 1989; Guitart, Beitner-Johnson, Marby, Kosten, & Nestler, 1992; Kosten, Miserendino, Chi, & Nestler, 1994, Kosten et al., 1997; Suzuki, George, & Meisch,

1988). Given this, we hypothesized that Lewis rats also would be more sensitive to sucrose and drug contrast. This proved to be the case. Thus, contrary to the account provided by Huang and Hsiao, we found that, following an unexpected downshift from 1.0 M to 0.1 M sucrose, Lewis rats exhibited a larger and more sustained successive negative contrast effect than Fischer rats (Freet, Tesche, Tompers, Riegel, & Grigson, 2006). In another set of studies (Grigson & Freet, 2000), Lewis rats also demonstrated larger anticipatory contrast effects than Fischer rats when saccharin predicted access to a high concentration of sucrose and greater avoidance of a saccharin cue when it predicted access to cocaine. The LiCl-induced CTA, however, did not differ between the two strains.

Huang and Hsiao (2008) took issue with these strain data. First, they suggested that, unlike our data, Foynes and Riley (2004) obtained greater LiCl-induced CTAs in Lewis versus Fischer rats when the drug was injected intraperitoneally (the rats consumed the LiCl US in our experiment). Examination of the Foynes and Riley data, however, make it clear that Lewis rats exhibited a greater LiCl-induced CTA than the Fischer rats with only 1 of 4 doses of the drug and then on only 1 of the 5 of the CS-US conditioning trials. In short, the case for differences in LiCl-induced CTAs between the Lewis and Fischer strains is weak, at best. Second, Huang and Hsiao give little credence to our cocaine data because, while Glowa et al. (1994) reported the same pattern of data with an 18 and 32 mg/kg dose of cocaine (i.e., greater suppressive effects in Lewis vs. Fischer rats), the strain effect was overridden by a high dose of the drug (e.g., 50 mg/kg). It is true that very high doses of cocaine will exert marked and equal suppressive effects, regardless of strain, possibly due to a floor effect. With this exception, however, both the suppressive effects of sucrose and cocaine are far greater in the Lewis rat. Finally, Huang and Hsiao discount the sucrose and cocaine strain data because another drug of abuse, morphine, exerts greater suppression of CS intake in Fischer than Lewis rats (Lancellotti, Bayer, Glowa, Houghtling, & Riley, 2001). We have found the same pattern of data with morphine, but we have shown that this strain effect is not due to a difference in sensitivity to a mu agonist (Liu & Grigson, 2005) and, instead, may be related to a profound increase in sensitivity of the Fischer rats to stimulation of the “aversive” kappa receptor (Wheeler et al., 2002). The interpretation of a conditioned reduction in CS intake, then, must take into account not only strain, but also the drug and the dose.

A final issue involves the data related to the underlying neuro-anatomical substrates. As described in our recent review (Grigson et al., 2008), lesions of the gustatory thalamus or cortex dissociate contrast from CTA in Sprague–Dawley rats. Bilateral electrolytic or ibotenic acid lesions of the gustatory thalamus have no impact whatsoever on the development of a LiCl-induced CTA (Flynn, Grill, Schulkin, & Norgren, 1991; Reilly & Pritchard, 1996; Scalera, Grigson, & Norgren, 1997). The same lesion, however, fully eliminates avoidance of the same taste cue when it predicts access to a preferred sucrose reward in the anticipatory contrast paradigm (Reilly, Bornovalova, & Trifunovic, 2004; Schroy et al., 2005) or when it predicts the administration of a 15 mg/kg dose of morphine (Grigson, Lyuboslavsky, & Tanase, 2000). Huang and Hsiao (2008) state that the results of Reilly and Trifunovic (1999) contradict our lesion data. In fact, the Reilly and Trifunovic study replicated our data showing that bilateral lesions of the gustatory thalamus block morphine-induced suppression of CS intake. Moreover, bilateral lesions of the insular cortex, the major projection region of the gustatory thalamus (Kosar, Grill, & Norgren, 1986a, 1986b), also disrupt the suppressive effects of morphine and lower doses of cocaine, but not those of LiCl (Geddes, Han, Baldwin, Norgren, & Grigson, 2008.; Mackey, Keller, & van der Koog, 1986). Taken together, these data show that the suppressive effects of sweets and drugs, but not LiCl, depend upon an intact gustatory thalamocoritical system.

In conclusion, the three experiments completed by Huang and Hsiao (2008) provide interesting data. Their interpretations, however, are limited by the absence of parallel studies using a putatively rewarding US (e.g., an assessment of backward conditioning and additivity using a sucrose US). The results of Experiment 1 could not address the reward comparison hypothesis because, as the authors demonstrated, greater CS intensity is associated with greater suppressive effects of sweets, drugs, and LiCl. The results of Experiment 2 showed that, like LiCl, amphetamine also supported backward conditioning in their paradigm. Contrast effects, however, also can occur in a retrograde fashion, leaving this as one of several viable interpretations. Experiment 3 was predicated on the assumption that a rewarding US would reduce the suppressive effects of an aversive LiCl US, while the suppressive effects of two aversive USs would be additive. The results of their experiment failed to support either prediction. Finally, contrary to their argument, considerable data indicate that LiCl-induced CTAs are less attenuated than are the suppressive effects of sweets or drugs by the use of sweet CSs and/or by the need for food or water. A contrast interpretation is possible for the furosemide data reported by Sorge et al. (2002). The selectively bred strain data are complicated, but Lewis rats clearly show greater cocaine- and sucrose-, but not LiCl-induced suppression of CS intake; and in Sprague–Dawley rats, these effects are mimicked following chronic morphine treatment (Grigson, Wheeler, Wheeler, & Ballard, 2001). Finally, lesions of the thalamocoritical taste pathway can block the suppressive effects of sweets and drugs, but not those induced by LiCl.

So, are drugs of abuse rewarding or aversive? Is the reward comparison hypothesis correct or is there more to the story? What about the task-dependent drug effects hypothesis? First, drugs of abuse do have both rewarding and aversive consequences. We hypothesize, however, that the relevant rewarding and aversive consequences do not occur simultaneously (as proposed by the task-dependent drug effects hypothesis), but that they occur sequentially in time. One, specifically, we propose that the reduction in CS intake is first mediated by a reward comparison mechanism, as the drug-associated taste cue pales in comparison to the potent rewarding properties of the drug. Two, with experience, however, the taste cue comes to elicit a conditioned compensatory state, such as cue-induced craving/withdrawal that is, itself, aversive (for a review, see Grigson et al., 2008). In support, avoidance of the taste CS is associated with a blunting of the accumbens dopamine response to the taste cue (Grigson & Hajnal, 2007), an elevation in circulating corticosterone (Gomez, Leo, & Grigson, 2000), and, if the cue is infused directly into the oral cavity (Wheeler et al., 2008), with frank aversive taste reactivity behavior (i.e., the rats will gape). Withdrawal induced by opiate blockers also is associated with blunted levels of dopamine in the nucleus accumbens (Shaham & Stewart, 1995), elevated levels of circulating corticosterone (Nunez, Foldes, Laorden, Milanes, & Kovacs, 2007), and aversive taste-reactivity following the intraoral infusion of a naloxone-associated taste cue (McDonald, Parker, & Siegel 1997). Three, the rate of the transition from reward comparison to the onset of the conditioned compensatory response depends upon the potency of the drug, the dose employed, the mode of administration (passive or active), and the vulnerability of the experimental subject. Thus, some Sprague–Dawley rats exhibit greater avoidance of the CS than others and greater avoidance of the taste cue is associated with greater cocaine self-administration and greater drug-seeking following extended abstinence (Grigson & Twining, 2002). Some drugs, like amphetamine, exhibit more of an “aversive” profile than morphine, for example. Among several drugs tested, Parker (1991) found evidence for aversive taste reactivity to a taste cue paired with a 2 mg/kg dose of amphetamine even when the drug was passively administered by the experimenter. Higher doses of some drugs also produce more of an “aversive” behavioral profile than others. For example, while lesions of the taste cortex fully eliminate the suppressive effects of low and high doses of morphine, the disruptive effect of the lesion on cocaine suppression are mixed. The lesion greatly disrupts the suppressive effects of a 10 mg/kg dose of cocaine, but the lesion effect is overridden by a 20 mg/kg dose of cocaine

(Geddes, 2008). In the self-administration paradigm, the disruptive effect of thalamic lesions was offset when the dose of cocaine was shifted from 0.165 to 0.33 mg/infusion iv (unpublished data). It is interesting to note that it is this same dose (0.33 mg/infusion) that supported the development of clear aversive taste reactivity following the intraoral delivery of the cocaine-associated CS (Wheeler et al., 2008). Four, finally, the greater this conditioned aversive state (e.g., the greater the number of gapes emitted following intraoral infusion of the CS), the faster the rat seeks a correction, resulting in a shorter latency to take drug, greater load-up behavior, and faster acquisition of drug-taking behavior (Wheeler et al., 2008).

Thus, we believe that drugs of abuse have potent rewarding properties and that the taste cue pales in comparison. Given the CNS effects of these drugs, however, with experience, the rat rapidly begins to prepare for drug delivery/infusion (Siegel & Ramos, 2002). The state associated with the onset of this conditioned compensatory response is aversive. The taste cue comes to elicit this aversive state and, by association, becomes even further devalued. The more aversive the state, the greater and the more rapid the correction. The correction (i.e., the relief from an aversive withdrawal state), then, is likely reinforcing via a negative reinforcement mechanism (Koob & LeMoal, 2008). Additional studies must be conducted to capitalize on the manipulations used by Huang and Hsiao (2008) if we are to functionally parse contrast from CTA and reward from aversion on a drug × dose × strain × experience basis. Such manipulations ultimately must employ the drug self-administration paradigm in order to test our hypothesis that the transition from avoidance to aversion (i.e., the onset of the conditioned compensatory response) will reliably predict the onset and intensity of addiction-like behaviors.

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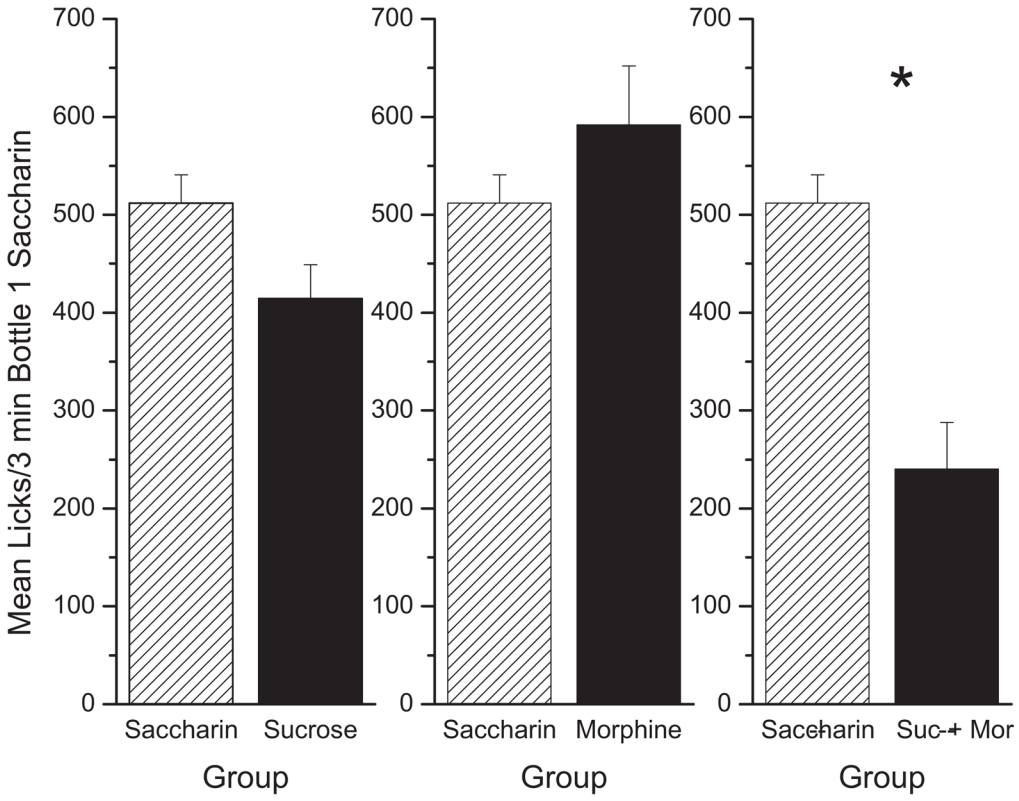

Figure 1.

Mean (± SEM) licks of first bottle 0.15% saccharin for rats in the control saccharin-saline + saccharin condition (Saccharin: hatched bars) compared to rats in the saccharin-saline + sucrose condition (Sucrose: left solid bar), saccharin-morphine + saccharin condition (Morphine: middle solid bar), or saccharin-morphine + sucrose condition (Suc + Mor: right solid bar). The data reflect the average taken across two days when testing occurred in a nondeprived state. Only the rats that received both morphine and sucrose exhibited a significant reduction in intake of the saccharin cue relative to the saccharin-saline + saccharin controls. * Indicates a significant difference.