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THEORETICAL REVIEW

Conditioned taste aversions: From poisons to pain to drugs of abuse

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Abstract Learning what to eat and what not to eat is fundamental to our well-being, quality of life, and survival. In particular, the acquisition of conditioned taste aversions (CTAs) protects all animals (including humans) against ingesting foods that contain poisons or toxins. Counterintuitively, CTAs can also develop in situations in which we know with absolute certainty that the food did not cause the subsequent aversive systemic effect. Recent nonhuman animal research, analyzing palatability shifts, has indicated that a wider range of stimuli than has been traditionally acknowledged can induce CTAs. This article integrates these new findings with a reappraisal of some known characteristics of CTA and presents a novel conceptual analysis that is broader and more comprehensive than previous accounts of CTA learning.

Keywords Palatability · Taste neophobia · Conditioned taste aversion · False positives

Introduction

A hungry animal chances upon something that might be edible. But is it safe to eat? If this unknown food is edible, its consumption will be beneficial. However, if the food contains a poison it might be the last meal the animal eats. If the animal survives the ingestion of the poisonous food (which will have caused some type of aversive systemic effect), it will have learned not to eat that particular food again. This phenomenon, termed *conditioned taste aversion* (CTA), is the focus of the present article.

The foregoing scenario is intended to emphasize the obvious: CTA defends animals (including humans) from the repeated ingestion of food-borne poisons. However, the CTA mechanism does not function alone. On first encounter with an unknown food, another phenomenon, taste neophobia, affords some protection from self-poisoning by limiting intake. Although the hungry animal of the preceding paragraph has taken an enormous risk by eating the unknown edible, survival is more likely because, if it was poisonous, only a small quantity was ingested. Thus, taste neophobia and CTA work in concert to protect us from the ingestion of tainted food.

Our goal in this article is not to provide an exhaustive catalogue of all aspects of CTA and taste neophobia, nor is it to review the voluminous literature on these phenomena. For such information, the following edited volumes and books are recommended: Barker, Best, and Domjan (1977); Braveman and Bronstein (1985); Bureš, Bermudez-Rattoni, and Yamamoto (1998); Milgram, Krames, and Alloway (1977); and Reilly and Schachtman (2009). Rather, our intention is to provide an overview of some recent findings from our laboratory that support a novel conceptual analysis that goes beyond the scope of the standard view of these phenomena. To achieve this goal, it is first necessary to present some of the defining characteristics of CTA and taste neophobia that provide the context within which our analysis is best appreciated.

Characteristics of CTAs

In nature, the food and the poison are contained in the same edible item. In the laboratory, these constituent elements are usually presented separately for purposes of experimental analysis.

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In the language of Pavlovian conditioning, CTA is viewed as the acquisition of an association between the taste (conditioned stimulus, CS) and the aversive systemic effects (unconditioned stimulus, US) of the food.[1] That said, it is important that we do not allow our reliance on terminology ("the CS" and "the US") to become so abstract that we lose sight of the phenomena we are trying to understand. CTA and taste neophobia are defense mechanisms that protect the feeding systems of human and nonhuman animals. In other words, these phenomena have functions that are governed by biology. With this perspective in mind, we are now in a position to appreciate some important characteristics of CTA learning and taste neophobia.

Generality Testifying to their purpose as a feeding system defense mechanism, CTAs are displayed by a vast array of animals. To give just a glimpse of this range, CTAs have been reported in slugs (Sahley, Gelperin, & Rudy, 1981), grasshoppers (Lee & Bernays, 1990), crabs (Wight, Francis, & Eldrige, 1990), cod fish (MacKay, 1974), crayfish (Arzuffi, Salinas-Loera, & Racotta, 2000), toads (Mikulka, Vaughan, & Hughes, 1981), snakes (Burghardt, Wilcoxon, & Czaplicki, 1973), hawks (Brett, Hankins, & Garcia, 1976), crows (Nicolaus, Cassel, Carlson, & Gustavson, 1983), bats (Ratcliffe, Fenton, & Galef, 2003), coyotes (Gustavson, Kelly, Sweeney, & Garcia, 1976), ferrets (Rusiniak, Gustavson, Hankins, & Garcia, 1976), rats (Garcia, Kimeldorf, & Koelling, 1955), cats (Kimeldorf, Garcia, & Rubadeau, 1960), monkeys (Matsuzawa, Hasegawa, Gotoh, & Wada, 1983), and, of course, humans (Garb & Stunkard, 1974; Klosterhalfen et al., 2000). Thus, one suspects that most animals, particularly those that have a varied and changeable diet, would show CTAs (for further discussion, see Garcia, Rusiniak, & Brett, 1977; Gustavson, 1977).

Conditioned stimulus Food, liquid or solid, has many orosensory properties (e.g., odor, taste, temperature, and texture), each of which can serve as a CS (see Riley & Clarke, 1977). In the nonhuman animal laboratory, taste is the most frequently employed CS. However, aqueous odors are at least as effective as aqueous tastes (Slotnick, Westbrook, & Darling, 1997). Furthermore, if a taste and odor are experienced together as a compound CS and followed by an illness-inducing US, the resulting conditioned odor aversion can be much stronger than the aversion that develops to the odor in the absence of the taste (Palmerino, Rusiniak, & Garcia, 1980; Rusiniak, Hankins, Garcia, & Brett, 1979). Such taste-potentiated odor aversions can be explained in terms of the taste stimulus gating the odor stimulus into the mechanism responsible for CTA learning (for a review, see Garcia, Lasiter, Bermudez-Rattoni, & Deems, 1985). However, subsequent research (Slotnick et al., 1997) has shown that the more salient stimulus (usually the taste, but possibly the odor) can potentiate the aversion accrued to a less salient stimulus (usually an odor, but possibly the taste). That is, stimulus salience, not modality (taste or odor), is an important determinant of the occurrence of taste-potentiated odor aversions. Taste-potentiated odor aversion is of particular relevance to the analysis of learning and conditioning, because it seems to be contrary to the cue-competition effects (e.g., overshadowing) that are typically found when two or more CSs are paired with a US (Kamin, 1969; Pavlov, 1927). Of course, taste-potentiated odor aversions are especially valuable because following acquisition of the food aversion, the food can be sniffed, rather than tasted, to determine whether it is poisonous.

In our everyday world, we are much more likely to experience compound CSs (a blend of two or more orosensory properties) than the pure, single-element CSs that are used for analytic purposes in the laboratory. Such CSs are termed *flavors*, which minimally involve an odor–taste compound. There are suggestions in the human literature that the odor constituent of the flavor can be as effective as the taste element in supporting aversion learning (e.g., Bartoshuk & Wolfe, 1990). Competition between the elements of a flavor CS for aversion learning is a well-documented issue in the nonhuman animal literature (for a review, see Batsell & Paschall, 2009), where one element can influence the strength of the aversion acquired to another element of a flavor compound CS. In the absence of appropriate control groups, the potential for cue-competition effects encourages caution when speculating about the nature of flavor aversion learning (i.e., which element accrues the strongest aversion) in both the human and nonhuman animal literatures.

Long-delay learning Biology dictates that taste is experienced before the systemic effects of the food. In addition, the slow absorption of some poisons will also contribute to a delay in the onset of the aversive systemic effects of the food-borne poison. A CTA mechanism constrained to function over CS–US delays measured in seconds would afford little survival value to us and other animals. It should not be surprising, then, that CTAs can be acquired if many minutes or even hours separate the CS from the US. In the controlled world of the laboratory, where all other parameters can be held constant, CS–US delays of 1–6 h support strong CTAs in nonhuman animals (e.g., Andrews & Braveman, 1975; Domjan & Bowman, 1974; Garcia, Ervin, & Koelling, 1966; McLaurin & Scarborough, 1963; Nachman, 1970; Revusky, 1968; J. C. Smith & Roll, 1967). Indeed, CTAs have been reported even when the CS and US were experienced 24 h apart (Etscorn & Stephens, 1973). In humans, CTAs have been reported with CS–US delays of up to 7 h (Garb & Stunkard, 1974; Logue,

[1] Alternative Pavlovian relationships for CTAs have been proposed, including CS–US–feedback (e.g., Garcia, 1989) and US–US (e.g., Goddard, 1999).

Ophir, & Strauss, 1981) under uncontrolled conditions (i.e., questionnaires).

One-trial learning An essential feature of any defense mechanism is that it should act rapidly. This is especially true with regard to the CTA mechanism, in that a failure to learn from the first experience with a poisonous food may be fatal. The literature is replete with examples of one-trial learning, including Andrews and Braveman (1975), Garcia et al. (1955), Matsuzawa et al. (1983), and Rozin (1986). A factor contributing to one-trial learning is the intensity/magnitude of the US: The more intense the US, the stronger the learning (e.g., Dragoin, 1971; Elkins, 1973; Green & Rachlin, 1976; Nachman & Ashe, 1973; Revusky, 1968). The most intense USs usually are not employed in laboratory-based research, they are used in the clinic. For example, treatments for cancer (involving chemotherapy and radiation therapy) constitute USs that are far beyond the intensity of the USs typically employed in research with nonhuman animals.

Early detection Not only can CTAs be acquired after a single CS–US pairing, but the mechanism is also exquisitely sensitive to the detection of low doses of the US, doses that might not otherwise exert any observable evidence of poisoning (e.g., Nachman & Ashe, 1973; J. C. Smith, 1971). This is one of the fundamentally important attributes of the CTA mechanism, because the earlier the detection of the US, the less poison will be ingested. When survival is at risk, the sooner the defense mechanism can be engaged, the better. On the other hand, this feature will also render the mechanism prone to false positives—better to err on the side of caution, and better to stay hungry than to eat a poisonous food.

Temporal order As we previously noted, biology dictates that we experience the taste before the systemic effects of the food. The CTA mechanism must be sensitive to the temporal order of the two events because causes precede effects. This may seem so obvious that there is no need for further discussion. However, that is not the entire story for a CTA. Thinking back to the scenario presented at the beginning of the Introduction, suppose that the poison in the food induced a coma shortly after the animal had finished eating. In this case, the aversive systemic effects of the food would not be experienced while the animal was awake. If a CTA was not acquired in this condition, then, on awakening, the animal, perhaps still hungry, might now eat a lethal amount of the same poisonous food. Alternatively, if a CTA was acquired, the animal would have learned not to eat that particular food again. Laboratory experiments have shown that animals can acquire CTAs when they are anesthetized after consuming the CS and during the entire duration of the US (e.g., Bermudez-Rattoni, Forthman, Sanchez, Perez, & Garcia, 1988; Burešová & Bureš, 1977; Rabin & Rabin, 1984; Roll & Smith, 1972). Such results are usually framed in terms of CTA being a process that can occur outside of consciousness or wakefulness. But such an analysis does not go far enough. The importance of these findings is that they demonstrate that the CTA mechanism is, in fact, blind to the origin of the US. This is a much underappreciated, but fundamentally important, attribute of the CTA mechanism. That is, the CTA mechanism merely links a prior taste experience with subsequent aversive systemic effects, irrespective of the cause of the latter.

In nonhuman animals, and indeed for most of human history, poisons have primarily gained entry into the body by ingestion. For nonhuman animals, reliance on temporal order is a considerable benefit, because it extends the range of the CTA defense mechanism. But for humans this attribute of the CTA mechanism can have disastrous consequences, because poisons can gain entry into our bodies in ways other than food consumption. For example, we know with absolute certainty that the food we ate did not cause the aversive systemic effects of chemotherapy or radiation therapy. Nevertheless, CTAs can be acquired in these circumstances (e.g., Bernstein, 1978, 1985; Jacobsen et al., 1993; for a review, see Scalera & Bavieri, 2009). Patients know that the CS did not cause the US, but that knowledge does not prevent them from developing CTAs to nonpoisonous foods. Thus, similar to the CTAs that develop in anesthetized laboratory animals, these acquired food aversions simply follow the principle of temporal order and are blind to the source of the US. Consequently, despite the fact that the food contains no toxins, its palatability decreases, and that food is shunned as an option in our diet. Furthermore, because the side effects of chemotherapy or radiotherapy are such powerful USs, the acquired CTAs can become a liability that threatens, rather than defends, the health and well-being of the individual. Inevitably, such CTAs detrimentally influence food intake, and malnutrition can become a major health concern. In the most extreme cases, the quality of life is so compromised that patients will postpone or quit chemotherapy or radiotherapy, despite the obvious life-threatening consequences (M. P. Carey & Burish, 1988; M. Miller & Kearney, 2004; Scalera & Bavieri, 2009).

Cue–consequence specificity If you develop a CTA following a meal in, say, a restaurant, you will attribute that aversion to something in the food rather than to the distinctive appearance of the place, the utensils you used, the plate upon which the food was served, your waiter, or your dining companions. In so doing, you have demonstrated cue-to-consequence specificity of learning. That is, the food you ate caused the aversive internal effects, not the other accompanying types of stimuli. This aspect of CTA learning was demonstrated in a classic study by Garcia and Koelling (1966; see also Domjan & Wilson, 1972; Garcia, McGowan, Ervin, & Koelling, 1968; V. Miller & Domjan, 1981a, 1981b). Thirsty rats were allowed

to drink a distinctive-tasting fluid that was accompanied by audiovisual stimuli and followed by either an aversive internal US (e.g., poison) or an aversive external US (pain of footshocks). Subsequent tests revealed that the rats developed a CTA with the internal US but not the external US. Conversely, the rats given the external US avoided drinking plain water in the presence of the audiovisual stimuli, but drank the tasty water in the absence of those external stimuli. Such findings demonstrate the obvious dichotomy that we and other animals more readily associate taste with internal aversive effects and audiovisual stimuli with external aversive effects.

Unconditioned stimulus CTA is a feeding system defense mechanism that protects us from the voluntary consumption of poisonous foods. So, the US is poison, which might be defined as a substance that tends to impair health or destroy life. The bodily effects of such USs are traumatic experiences. In the literature, the effect of the US has been described in terms such as gastrointestinal (or visceral) discomfort (or distress), illness, malaise, nausea, sickness or toxicosis, or more generally, *gastrointestinal malaise* (GIM). To be maximally effective, the CTA mechanism must be very widely tuned, because poisons come in myriad forms and types that have numerous modes of action and disparate pharmacological effects. Thus, GIM is an umbrella term for any kind of illness that can be caused by food-borne poisons. In the laboratory, the most common agent used to produce GIM is lithium chloride (LiCl).

As we previously discussed, because temporal order overrides causality in CTA learning, events that are unrelated to prior food intake can induce CTAs. However, these USs may do so because they cause aversive systemic effects (i.e., GIM). USs in this category include various types of radiation (Garcia et al., 1955; Rabin & Hunt, 1986; Revusky, 1968; J. C. Smith, 1971); chemotherapy (Bernstein & Webster, 1980; Burish, Levy, & Meyerowitz, 1985; Scalera & Bavieri, 2009); motion sickness or, more generally, vestibular disorientation (Arwas, Rolnick, & Lubow, 1989; Braun & McIntosh, 1973; Fox, Corcoran, & Brizzee, 1990; Hutchison, 1973); high-strength magnetic fields (Cason, Kwon, Smith, & Houpt, 2010; Houpt & Smith, 2009); and running and swimming (Boakes & Nakajima, 2009; Lett & Grant, 1996; Nakajima & Katayama, 2014).

Palatability *Palatability* is the affective value of a taste/food (Berridge, 2000; Breslin, Spector, & Grill, 1992; Steiner, Glaser, Hawilo, & Berridge, 2001): You eat foods that you like, and do not eat foods that you dislike. Two distinct methodologies have been developed to measure palatability in nonhuman animals: the taste reactivity test and lick pattern analysis. These complementary approaches have unique sets of strengths and weaknesses that dovetail to offer analytical tools for virtually any situation. In the following discussion, we will briefly describe the basics of the taste reactivity test and lick pattern analysis, conceptualizations of palatability, and applications to the evaluation of conditioned changes in taste palatability.

The taste reactivity test involves experimenter-controlled infusions of a tastant directly into the mouth while, concomitantly, the evoked stereotypical orofacial reactions are recorded (e.g., Grill & Norgren, 1978b). These responses can be categorized as either ingestive or aversive (for reviews, see Berridge, 2000; Steiner et al., 2001). Indicative of positive hedonic value, *ingestive* responses include mouth movements, tongue protrusions, and lateral tongue protrusions. Indicative of negative hedonic value, only one *aversive* orofacial response has been identified in the rat—namely gaping, which is analogous to retching or vomiting (Travers & Norgren, 1986). It should be noted that the mild to moderate aversive orofacial responses that have been identified in other species (e.g., midface grimacing, found in great apes and humans; Steiner et al., 2001) have yet to be documented in the rat. Thus, the absence of gaping does not necessarily mean the absence of aversion; care must therefore be exercised to prevent this "blind spot" from influencing data interpretation.

With regard to lick pattern analysis, when voluntarily drinking, rats tend to produce sustained runs (termed *clusters*) of licks that are interrupted by pauses. A number of measures can be extracted by analyzing the temporal patterns of licking, including total licks, lick rates across various time intervals, interlick interval, intercluster interval, number of clusters, and cluster size. Analysis has revealed that cluster size and the initial lick rate are sensitive measures of taste palatability. For an unconditionally aversive taste stimulus (e.g., quinine), both lick cluster size and the initial lick rate decrease monotonically as concentration increases (e.g., Hsiao & Fan, 1993; Spector & St. John, 1998). On the other hand, for an unconditionally preferred taste stimulus (e.g., sucrose), these two variables increase monotonically as concentration increases. Importantly, lick cluster size and the initial lick rate do not reflect the amount consumed, which bears an inverted-U relationship with the taste concentration (e.g., Davis & Smith, 1992). This pattern of results suggests that both lick cluster size and initial lick rate are independent of the volume consumed but faithfully reflect the hedonic value of taste stimuli (for discussions of lick pattern analysis and palatability assessment, see Davis, 1989, 1998; Davis & Levine, 1977; Dwyer, 2012; Lin, Arthurs, & Reilly, 2014).

Traditionally, palatability is viewed as ranging along a single continuum (or dimension) from positive to negative (e.g., Le Magnen, 1987; Young, 1977), a conceptualization that readily applies to data obtained with the taste reactivity test and lick pattern analysis. A second account of palatability arose when certain taste stimuli were found to elicit mixtures of ingestive and aversive unconditioned responses in the taste

reactivity test (Berridge & Grill, 1983, 1984). These results were interpreted as evidence that palatability varies along two independent dimensions (ingestive and aversive), such that changes in the occurrence of ingestive responses have no bearing on aversive responses, and vice versa. However, later work from this group suggested that palatability is best viewed as a single dimension, at least in the context of conditioned shifts in palatability such as CTA (Breslin et al., 1992). According to this one-dimension account, shifts in palatability occur along a continuum, with a decline in ingestive responses transitioning into an increase in aversive responses, and vice versa. Except where otherwise noted, conditioned changes in the occurrence of taste reactivity responses are interpreted below within the framework of a one-dimension account of palatability.

Turning now to the standard taste reactivity design for CTA, a brief intra-oral infusion of the taste stimulus is followed by the induction of GIM, and these CS–US pairings are spaced a minimum of 24 h apart. A CTA is revealed, across trials, as a reduction in ingestive responses and the occurrence of aversive responses (e.g., Berridge, Grill, & Norgren, 1981; Eckel & Ossenkopp, 1996; Flynn, Grill, Schulkin, & Norgren, 1991; Grill & Norgren, 1978a). An alternative design involves tracking changes in the frequency of responses across "long-duration" trials. In a classic article, Spector, Breslin, and Grill (1988; see also Breslin et al., 1992) employed this approach and demonstrated, using 30-s infusions of a taste CS given once every 5 min for a 30-min trial, that the acquisition of an LiCl-induced CTA involves a decrease in the frequency of ingestive responses and the appearance of aversive responses. The development of strong CTAs is readily identified in these designs because of the occurrence of gaping. Weaker CTAs—those that do not produce gapes—are manifest as a conditioned reduction in ingestive responses. As we noted above, the absence of gapes does not always indicate the absence of a CTA.

One of the advantages of lick pattern analysis is that voluntary consumption and taste palatability can be monitored simultaneously. Using the traditional CTA procedure, thirsty rats are given access to a novel taste solution, followed by GIM. In addition to the expected reduction of CS intake, lick pattern analysis shows that the palatability of the associated taste CS conditionally decreases across learning trials (e.g., Arthurs, Lin, Amodeo, & Reilly, 2012; Baird, St. John, & Nguyen, 2005; Dwyer, 2009; Dwyer, Boakes, & Hayward, 2008; Lin, Arthurs, & Reilly, 2013). To illustrate, Fig. 1 depicts data from Lin et al. (2013), in which CS intake (Fig. 1A), lick cluster size (Fig. 1B), and initial lick rate (Fig. 1C) were all significantly reduced for the saccharin CS following contingent pairings with the LiCl US; the control group, which received isotonic saline injections instead of LiCl, showed no reduction in CS palatability and intake.

Lick pattern analysis is inherently one-dimensional, varying downward along a continuum from a high frequency of licks until voluntary consumption no longer occurs. The

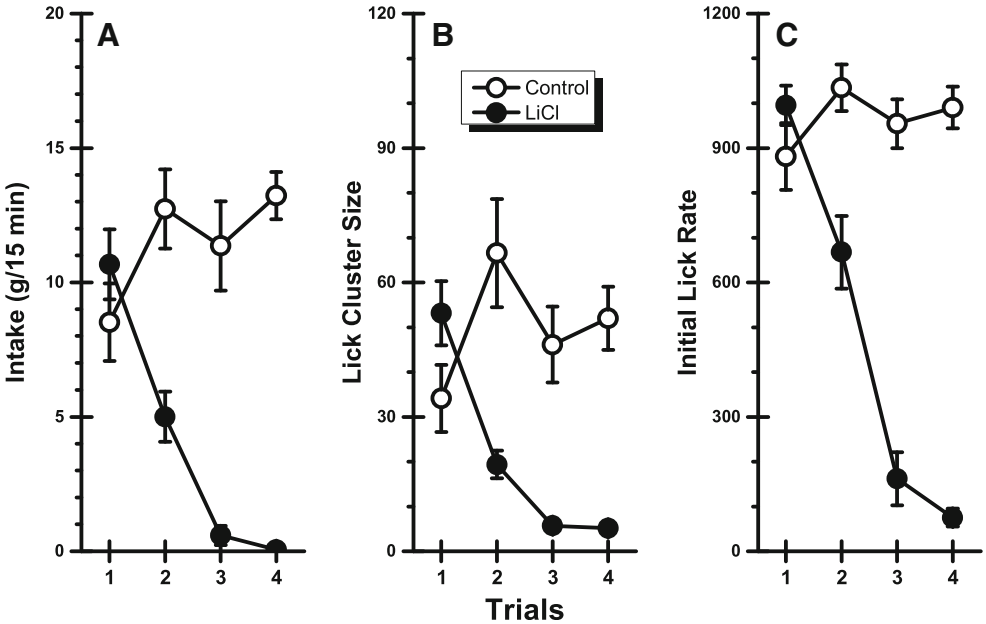

Fig. 1 Mean (± *SE*) conditioned stimulus (0.1 % saccharin) directed performance across three conditioning trials and one taste-only trial in rats given contingent injections of either isotonic saline (Control) or lithium chloride (LiCl; 0.075 M at 5 ml/kg): (A) intake, (B) lick cluster size, and (C) initial lick rate (total licks during the first 3 min following the first lick). Figure is redrawn from Lin et al. (2013)

acquisition of a CTA can be observed as a conditioned reduction in cluster size and initial lick rate. Obviously, lick pattern analysis is dependent upon voluntary drinking. When a CS becomes so aversive as to preclude voluntary ingestion, contact is lost with the absolute strength of the aversion. Beyond this point, the strength of the CTA can be evaluated only with the taste reactivity test following intra-oral infusions of the highly aversive CS. Thus, taste reactivity is an invaluable method to assess CTAs that are so strong that the CS will no longer be sampled voluntarily.

Whether using the taste reactivity test or lick pattern analysis, CTAs are defined by a conditioned reduction in the palatability (or hedonic value) of the associated taste CS. Like other researchers (e.g., Feurté, Nicolaidis, & Berridge, 2000; Garcia et al., 1970; Pelchat & Rozin, 1982), we view CTA as a palatability downshift mechanism and consider the traditional index of CTA, reduced intake, to be a consequence of the conditioned palatability downshift. Thus, in the context of CTA acquisition, reductions of intake can be viewed as a good proxy for the conditioned reduction in taste palatability.

Characteristics of taste neophobia

Recalling the scenario from the opening paragraph of the Introduction, the individual was wary about eating an edible of unknown taste and content. Traditionally, this taste neophobia effect is conceptualized as an innate avoidance response that limits intake on first encounter, due to fear that the edible may contain poison (Barnett, 1958; Corey, 1978; Domjan, 1977; Lin & Reilly, 2012; Rozin, 1976). If the edible is not poisonous (i.e., no aversive systemic consequences occur in the minutes to hours that follow ingestion), intake of the new food increases across subsequent encounters, until asymptote is achieved for the now familiar and safe item (i.e., taste neophobia habituates). If, on the other hand, the edible is poisonous, and if the animal survives that encounter, the CTA mechanism will ensure that the poisonous food is not eaten again.

Taste neophobia plays a prominent role in food selection among humans (e.g., Birch & Marlin, 1982; Kauer, Pelchat, Rozin, & Zickgraf, 2015; Pliner & Salvy, 2006) and nonhuman animals (e.g., Barker, Best, & Domjan, 1977; Itani, 1958), particularly those with a varied and changeable diet. In humans, taste neophobia is a major issue, especially in young populations (e.g., Dovey, Staples, Gibson, & Halford, 2008), for whom it can become problematic, by limiting the inclusion of nutritious novel foods into the developing diet (e.g., Cooke, Wardle, & Gibson, 2003; Falciglia, Couch, Gribble, Pabst, & Frank, 2000). Indeed, disordered (i.e., exaggerated) taste neophobia may contribute to aspects of the avoidant/restrictive food intake disorder recently described in the DSM-5 (American Psychiatric Association, 2013).

Like CTA, taste neophobia limits food intake to prevent poison from entering the internal milieu. In the case of CTA, the danger is real, whereas in taste neophobia the threat is unknown, but nonetheless highly motivating. CTA involves a learned downshift in the palatability of the taste CS. Does taste neophobia modulate palatability or, alternatively, is taste neophobia an avoidance response in which palatability has no role? Surprisingly, this question has received little empirical attention, particularly in the nonhuman animal literature, in which taste neophobia typically is quantified by monitoring the amount consumed of a novel substance. Using lick pattern analysis, we recently discovered that taste neophobia does indeed modulate palatability (Lin, Amodeo, Arthurs, & Reilly, 2012). For instance, rats tested with a concentrated solution of saccharin not only drank little on first exposure (see Fig. 2A), but we found that the palatability (i.e., the lick cluster size, Fig. 2B, and initial lick rate, Fig. 2C) of the novel solution was extremely low. Over subsequent exposures, as the rats became more and more experienced with the benign solution, intake and palatability increased, to expose the true magnitude of the substantial unconditioned suppression of intake and palatability caused by taste neophobia. Of course, asymptotic performance is governed by a variety of factors (e.g., hydration, taste). However, it appears that unconditioned fear suppresses palatability and intake during the initial encounter with a novel taste. Thus, taste neophobia not only suppresses palatability (which we believe drives intake) on initial encounter, but the pleasure of drinking or eating increases as taste neophobia habituates and the previously novel, potentially dangerous substance becomes seen as both familiar and safe.

In addition to suppressing palatability and intake, the state of fear that is aroused by consumption of the unknown edible may also render the individual particularly vigilant about any changes in their internal milieu (e.g., Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004; Paulus & Stein, 2006). That is, in the minutes and hours that follow consumption, the individual is waiting to discover whether the unknown food was poisonous. We propose that taste neophobia primes the CTA mechanism to become engaged when suspicions of toxicity are aroused.[2] This is how CTAs are so readily acquired to novel, poisonous foods. On the other hand, if there are no aversive postingestive consequences, the palatability of the benign food increases. If you know that a familiar food is not poisonous, it is much more difficult (i.e., requires more CS–US pairings) to acquire a CTA to the taste of that food, a

[2] Alternatively, one might say that taste neophobia lowers the decision threshold for the detection of aversive systemic effects, which allows the CTA mechanism to be triggered earlier than otherwise would be the case. Irrespective of terminology, the quicker the detection of the food-borne poison, the less likely a fatal dose will be ingested. That is, reliance on certainty (rather than suspicion) that a poison has gained entry into the internal milieu is counterproductive in CTA learning.

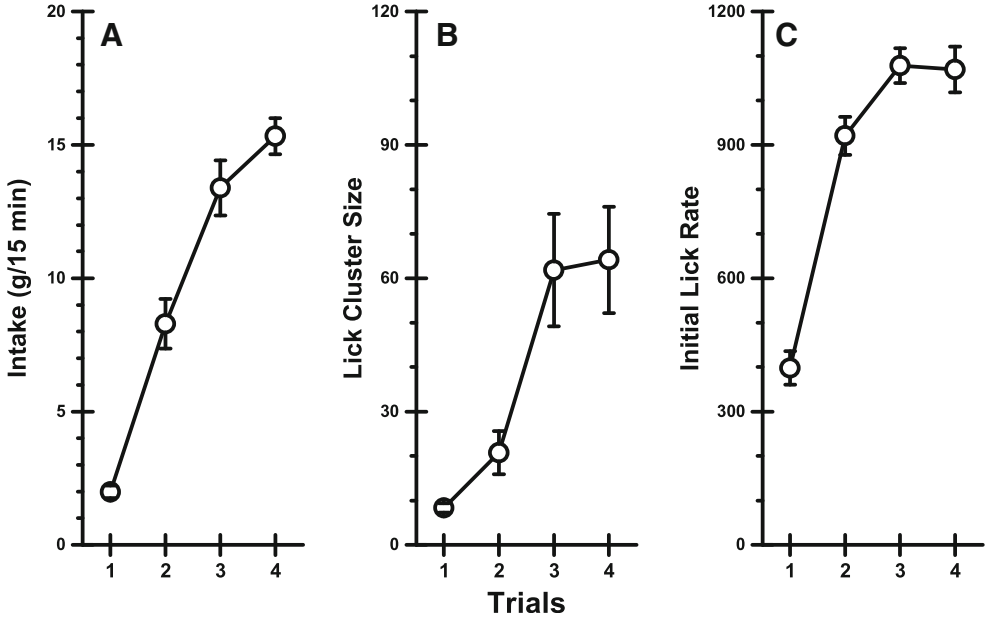

Fig. 2 Mean (± *SE*) performance during the four 15-min taste neophobia trials (0.5 % saccharin): (A) intake, (B) lick cluster size, and (C) initial lick rate (total licks during the first 3 min following the first lick). Figure is redrawn from Lin, Amodeo, et al. (2012)

well-known phenomenon termed *latent inhibition* (for reviews, see Lubow, 1989, 2009).

The taste neophobia priming effect on the CTA mechanism may go further than is usually appreciated. That is, because the CTA mechanism is blind to the origin of the US (see the Temporal Order section above), taste neophobia primes the mechanism to the most obvious cause—the most recently consumed unfamiliar edible. This feature not only increases survival value, it also renders the CTA mechanism prone to false positives. In our view, false positives are an essential feature of a system in which a single failure to detect a poison may have fatal consequences.

CTAs and pain

Pain may be classified as either external or internal, depending on its source. As we mentioned in the section on cue–consequence specificity, external pain (in the form of footshock) is much less readily associated with a taste CS than is GIM. However, evidence of such "selective associations" does not mean that external pain cannot guide intake. Indeed, Garcia, Kovner, and Green (1970) reported that taste intake could be suppressed by repeated contingent pairings with footshocks. For the present purposes, the critical issue concerns the nature of pain-induced learning. So far, we have focused on CTA learning, which involves a conditioned reduction of CS palatability and the consequent suppression of intake. A qualitatively different form of taste learning, which to avoid confusion we will term *taste avoidance learning* (TAL), involves a conditioned reduction of CS intake in the explicit absence of any change in the palatability of the taste CS. So, is pain-induced taste suppression an instance of CTA or TAL?

Various lines of evidence have indicated that external pain supports TAL. To begin with, Garcia and colleagues found that footshock-induced intake suppression is highly context-specific. That is, rats refused to consume the shock-paired taste in the context where original learning had occurred, but drank the taste CS in other places; this context-specific effect is absent with a GIM-paired taste CS (Garcia et al., 1970). In a later study from Garcia's laboratory, Brett (1977) elegantly demonstrated that taste palatability plays no role in shock-induced taste suppression. In this experiment, a footshock was delivered at the midpoint of 60-s taste trials. Following training, the rats suppressed drinking during the first half of each trial, but eagerly consumed the taste CS over the final 30 s. This pattern of results indicates that a taste CS paired with an external pain US can become a danger signal that suppresses intake (see also Garcia, Brett, & Rusiniak, 1989). Finally, Pelchat, Grill, Rozin, and Jacobs (1983), using taste reactivity methodology, found no positive evidence that repeated taste–footshock pairings had any influence on the palatability of the taste CS. Overall, we conclude that external pain does not cause CTAs. Rather, external pain supports TAL,[3] which involves intake suppression but no learned changes in taste palatability.

Like external pain USs, internal pain USs are known to suppress intake of the associated taste CS. For example, Lett (1985) found that contingent administration of gallamine (which induces muscular paralysis and pain by blocking

[3] We suggest that an alternative interpretation is that, for external pain USs like shock, the behavior of licking is being punished.

cholinergic transmission at the neuromuscular junction; Cull-Candy & Miledi, 1983; Mishra & Ramzan, 1992) suppressed intake of the associated taste CS. Similarly, hypertonic saline (a laboratory model of visceral pain; Giesler & Liebeskind, 1976) is an effective US that can suppress the intake of a taste CS (e.g., Nachman & Ashe, 1973; Sakai & Yamamoto, 1997). As with external pain, the issue is whether the taste learning established with an internal pain US is CTA or TAL.

To the best of our knowledge, Pelchat et al. (1983) was the first study that used naïve animals to examine whether taste palatability changes consequent to contingent administrations of internal pain. In this experiment, the rats were required to drink 40 % lactose, the taste of which served as the CS, whereas discomfort and pain in the gastrointestinal tract (caused by malabsorption of the lactose) functioned as the US. The results revealed no between-group differences in either ingestive or aversive taste reactivity responses, although lactose intake was suppressed to ~0.5 ml in the experimental group, relative to ~7.0 ml in the control subjects. On the basis of these results, Pelchat et al. claimed that internal pain supports TAL, not CTA. However, confidence in this interpretation is diminished by certain design choices (for more detailed discussion, see Lin et al., 2013). For instance, an unconventional procedure was used that involved monitoring taste reactivity responses during voluntary drinking, instead of the standard intra-oral infusions of small volumes of the taste solution.[4] Furthermore, the extremely low amounts of lactose voluntarily consumed during the test trial limited the opportunity to observe the evoked taste reactivity responses. It should be noted that Pelchat et al. defined CTA purely in terms of an increase in aversive taste reactivity responses. Thus, the absence of such behaviors was taken as evidence of the absence of CTA. Interestingly, the authors acknowledged that, "we might not be able to detect a decrease in hedonic value that did not involve a reversal in sign because orofacial response is a binary indicator of a presumably continuous underlying variable" (p. 150). These considerations encourage additional research to evaluate the nature of taste learning that is induced with internal pain USs.

Thirty years later, Lin et al. (2013) addressed this issue by using lick pattern analysis to assess taste palatability when gallamine (10 mg/kg) and hypertonic saline (1.0 M) were used as the USs. These injectable USs were favored over ingested lactose (the use of which presents design and practical problems, not least of which is the loss of experimental control over the dose of lactose that each rat receives) to afford direct comparability with LiCl-induced CTAs, because the only between-experiment difference between these USs concerns the nature of the postingestive consequence (internal pain vs. GIM).

As expected, contingent administrations of gallamine or hypertonic saline suppressed intake of the associated taste CS (0.1 % saccharin) across conditioning trials. More importantly, this research revealed that the intake suppression was accompanied by a reduction in the palatability of the taste CS. As is shown in the gallamine data summarized in Fig. 3, rats that received CS–US pairings significantly decreased their intake (panel A), lick cluster size (panel B), and initial lick rate (panel C), relative to control subjects given CS–no-US presentations. The results of Lin et al. (2013) provide, for the first time, clear and definitive evidence that internal pain USs, functioning like GIM to cause a conditioned reduction in the palatability of the associated taste CS, support CTA, not TAL.

We should note that their study provided some suggestion that internal pain may not be as efficient as GIM in producing CTAs. Specifically, gallamine and hypertonic saline each required more CS–US pairings to establish the same CTA strength as LiCl (Lin et al., 2013). Although the different rates of CTA acquisition may simply reflect differences in the magnitudes of the different USs (i.e., they may represent a scaling issue), the pattern of results raises an interesting hypothesis that the CTA mechanism may be more sensitive to USs that directly act in and around the gastrointestinal tract. For USs, like internal pain, that work more distal from the gastrointestinal tract, we speculate that the CTA mechanism may be engaged, but in a less efficient manner.

The finding that internal pain by itself causes CTA learning provides empirical evidence that the CTA mechanism is a widely tuned system that is capable of defending us from the ingestion of foods that have adverse effects on our bodies that include, but are not restricted to, GIM.

CTAs and drugs of abuse

One of the most intriguing findings in the literature is that drugs of abuse can serve as USs to suppress the intake of a taste CS. These drugs include amphetamine, cocaine, ethanol, morphine, and nicotine (e.g., Berger, 1972; Cappell & LeBlanc, 1971, 1973; Cappell, LeBlanc, & Endrenyi, 1973; R. J. Carey, 1973; Kumar, Pratt, & Stolerman, 1983; Nachman, Lester, & Le Magnen, 1970; Riley, Jacobs, & LoLordo, 1978; Vogel & Nathan, 1975). It should be noted that such drugs produce no obvious signs of GIM. Indeed, psychoactive drugs suppress CS intake at doses that are known to produce rewarding effects in other behavioral procedures (e.g., conditioned place preference and self-administration tasks; Bardo & Bevins, 2000; Jaffe, 1970; Tzschentke, 1998, 2007; Weeks, 1962) and are used recreationally by humans, who voluntarily inject, smoke, snort, or swallow their drugs of choice.

[4] Taste reactivity is rarely used with voluntary intake, because ingestive and aversive responses can only occur in the pauses between clusters of licks. That is, licking and taste reactivity responses are mutually exclusive behaviors.

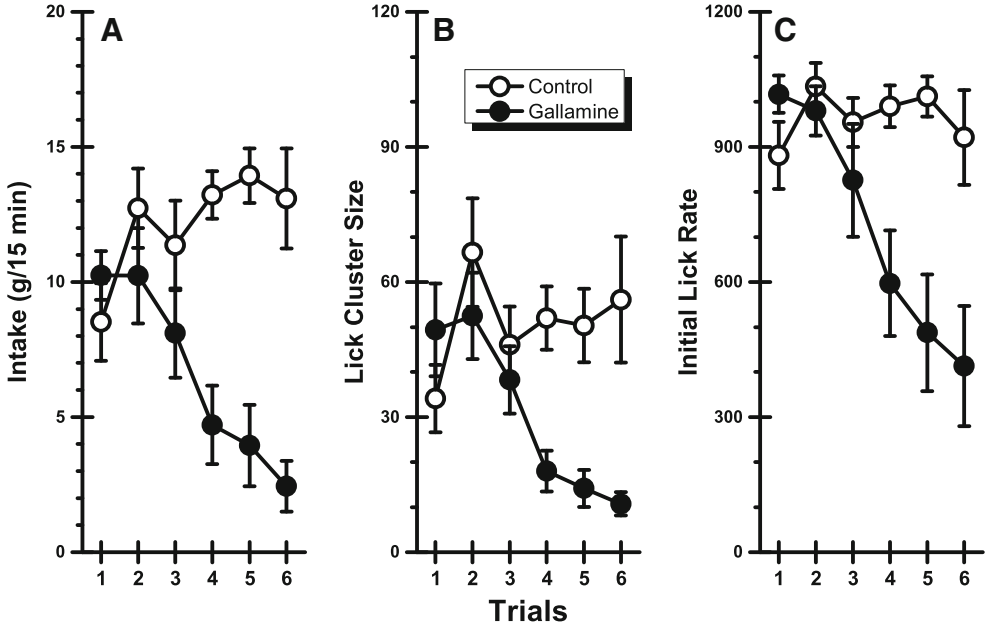

Fig. 3 Mean (± *SE*) conditioned stimulus (0.1 % saccharin) directed performance across five conditioning trials and one taste-only trial in rats given contingent injections of either isotonic saline (Control) or gallamine hydrochloride (Gallamine, 10 mg/kg): (A) intake, (B) lick cluster size, and (C) initial lick rate (total licks during the first 3 min following the first lick). Figure is redrawn from Lin et al. (2013)

As is indicated in the titles of many of the original articles, the phenomenon was interpreted as a CTA because, just like poisons, drug USs suppressed intake of the taste CS. But how could rewarding drugs also cause aversions? One answer to this question is that abused drugs have both rewarding and aversive properties, with the latter being responsible for CTA learning (e.g., Cunningham, 1979; Ettenberg & Geist, 1991; Goudie, 1979; Huang & Hsiao, 2008; Verendeev & Riley, 2012, 2013; N. White, Sklar, & Amit, 1977; Wise, Yokel, & DeWit, 1976). However, not until the emergence of techniques that could directly monitor taste palatability could the nature of drug-induced taste suppression be addressed empirically. Thus, the question has now become: Do drug-of-abuse USs function like GIM and internal pain to induce CTAs or, alternatively, do they function like external pain, and induce TAL?

The most programmatic research undertaken to answer this question began in the 1980s, when Parker and colleagues initiated a series of studies using rats and the taste reactivity test to assess the palatability of a taste CS paired with a drug US. These experiments employed a diverse array of psychoactive drugs, including amphetamine (Davies & Wellman, 1990; Parker, 1982, 1988, 1991; Parker & Carvell, 1986; Zalaquett & Parker, 1989), apomorphine (Parker & Brosseau, 1990), cocaine (Mayer & Parker, 1993; Parker, 1993), ethanol (Davies & Parker, 1990; Parker, 1988), lysergic acid diethylamide (Parker, 1996), methamphetamine (Parker, 1993), methylphenidate (Parker, 1995), morphine (Parker, 1988, 1991), naltrexone (Parker & Rennie, 1992), nicotine (Parker, 1991; Parker & Carvell, 1986), pentobarbital (Parker, 2003; Parker, Limebeer, & Rana, 2009), phencyclidine (Parker, 1993), and Δ^9-tetrahydrocannabinol (Parker & Gillies, 1995). In all of these studies, the same result was obtained: The drug US (at doses known to be rewarding in other tasks) significantly suppressed intake and ingestive taste reactivity responses, but there was no significant postconditioning evidence of gaping. Applying a gaping-dependent definition of CTA, Parker and colleagues (e.g., Parker, 1995, 2003, 2014a, 2014b; Parker et al., 2009) interpreted the obtained pattern of results as evidence that drugs of abuse, at otherwise rewarding doses, induce TAL, not CTA.

As similar evidence has accumulated, this aversion–avoidance account of taste learning has gained widespread acceptance. Indeed, the interpretation that drug-of-abuse USs do not influence the palatability of the associated taste CS is considered so well-founded that it has become the starting point for alternative accounts of drug-induced taste suppression. For instance, Grigson and colleagues (e.g., Grigson, 1997, 2008; Grigson, Twining, Freet, Wheeler, & Geddes, 2009) have argued that drugs of abuse have no aversive properties and that the suppression of CS intake is actually the product of a reward comparison in which the higher-valued drug US suppresses intake of the lower-valued taste CS. Thus, the reward comparison hypothesis is firmly anchored in

acceptance of Parker's analysis that drug USs do not support CTA learning.

Notwithstanding repeated replication of the basic taste reactivity finding, a reexamination of that literature and recent research has cast doubt on the veracity of the TAL interpretation of drug-induced taste suppression. It will be recalled that rats show only one aversive orofacial response, gaping; they do not display the midface grimace that is indicative of mild to moderate aversiveness in primates.[5] Given (1) that gaping is indicative of an extreme level of aversion and (2) that the drug doses involved are relatively low, it should not be surprising that drug USs may not support conditioned gaping to the associated taste CS. Furthermore, as we have noted with regard to GIM-induced CTAs, the absence of gaping does not necessarily indicate the absence of aversion. Indeed, as was shown in the taste reactivity experiment of Spector et al. (1988), the reduction of CS palatability that defines CTA starts with a conditioned reduction of ingestive taste reactivity responses that is followed, in the case of strong CTAs, by the appearance and increased occurrence of aversive taste reactivity responses. Although drug USs may not reach the level of aversion necessary to cause gaping, they do significantly suppress the occurrence of ingestive reactions to a taste CS (e.g., Parker, 1988, 1991, 1993, 1996; Parker & Brosseau, 1990; Parker & Carvell, 1986). But, for Parker and colleagues conditioned downshifts in ingestive taste reactivity responses (which can be numerically substantial) do not constitute evidence of CTA, which they define exclusively by the occurrence of gaping. By Parker's interpretation, then, the weakest detectable CTAs are those that produce low levels of gaping—stronger CTAs can, presumably, be defined in terms of higher levels of gaping and the emergence of aversive somatic responses. However, because gaping is analogous to retching or vomiting (Travers & Norgren, 1986), even a low level of gaping would seem to be evidence of a very strong CTA. Thus, irrespective of the nature of the US (i.e., drug of abuse, internal pain, or GIM), this implicitly two-dimensional analysis of conditioned palatability changes would seem to deny that mild to moderate CTAs are possible, and consequently must view CTA as an all-or-none phenomenon in the rat. To address this interpretational issue empirically, we turned to lick pattern analysis to reexamine whether a drug-of-abuse US supports a conditioned shift in the palatability of the CS.

In a series of experiments we found that, irrespective of the innate initial value of the CS (preferred, neutral, or nonpreferred), drug USs (i.e., amphetamine, morphine) not only suppress CS intake, but also induce a conditioned reduction in the palatability of the CS (e.g., Arthurs et al., 2012; Lin, Arthurs, Amodeo, & Reilly, 2012). Figure 4 shows data from one of these experiments, in which sodium chloride served as the CS and amphetamine the US (Lin, Arthurs, et al., 2012). As is shown in the figure, amphetamine suppressed the amount consumed (panel A), lick cluster size (panel B), and initial lick rate (panel C).

We interpret these experimental results as evidence that, just like GIM-based USs, drug-of-abuse USs support CTA, not TAL. Indeed, we believe drug-induced CTAs can be interpreted in terms of the functioning of the two feeding system mechanisms that have evolved to protect us from the ingestion of food-borne poisons.

Where are we now?

Taste neophobia and CTA work in concert to protect humans and other animals from ingesting poisons. In nature, the poison is in food. When an unknown, potentially poisonous food is encountered, taste neophobia primes the CTA mechanism to be vigilant for subsequent signs of poisoning. Our research has demonstrated that CTA is a broadly tuned mechanism that is responsive to many signs of poisoning, including those generated by GIM and internal pain. After poisoning, CTA acts to prevent further intake of the tainted food by modifying the palatability of the associated taste. That is, CTA is a palatability downshift mechanism. In the case of novel foods, taste neophobia not only primes the CTA mechanism into action, but also holds the palatability of the taste at a significantly lower level than if the taste were known to be familiar and safe. As we noted in the Temporal Order section, the CTA mechanism is blind to the origin of the US—the mechanism simply links a prior taste experience with later aversive systemic effects, regardless of their origin. This is why CTAs can develop in anesthetized animals, or in people who certainly understand that the food did not cause their GIM (e.g., chemotherapy patients). By rendering the poisonous food unpalatable, or even disgusting, the CTA mechanism ensures that the food will be rejected in future encounters.

But, how are drug-induced CTAs to be explained?

We take drugs because they make us feel good, they give us pleasure, and they are rewarding. In short, drugs have positive effects on us, and consequently, they have abuse potential. An important caveat, of course, is that these positive effects of drugs are dose-dependent. At higher doses, drugs are aversive and increasingly toxic, as indicated by, for example, the development of conditioned place aversions (Barr, Paredes, & Bridger, 1985; Bechara, Zito, & Van Der Kooy, 1987; Bienkowski, Iwinska, Piasecki, & Kostowski, 1997;

[5] Rats do show additional aversive taste reactivity responses, but these somatic behaviors (e.g., chin rubbing, headshaking, face washing, flailing of the forelimbs, and paw wiping) occur after, not before, gaping (e.g., Grill, 1985).

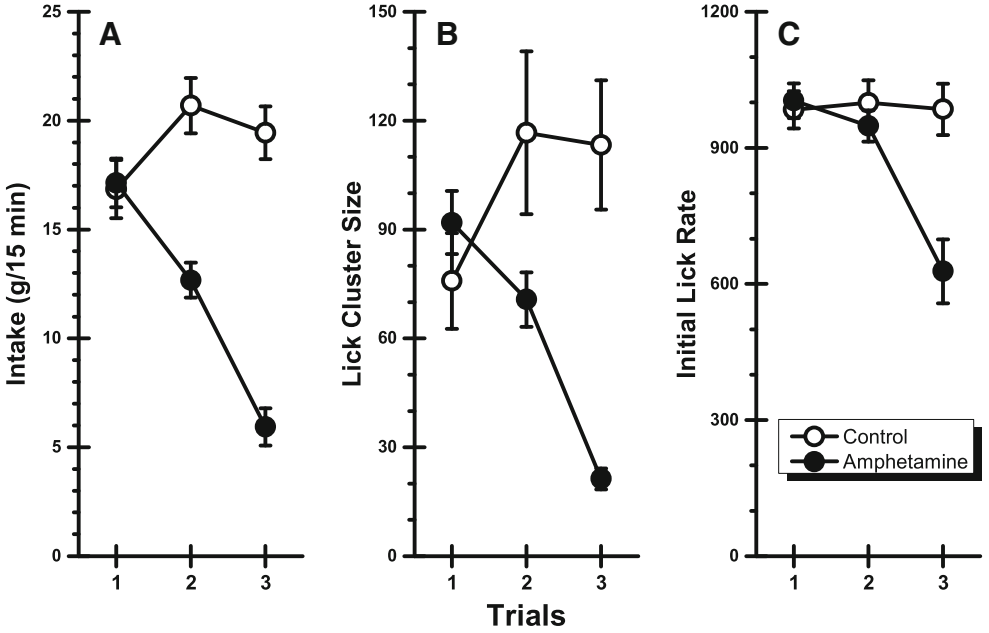

Fig. 4 Mean (± *SE*) conditioned stimulus (0.1-M sodium chloride) directed performance across two conditioning trials and one taste-only trial in rats given contingent injections of either isotonic saline (Control) or D-amphetamine sulfate (Amphetamine, 1 mg/kg): (A) intake, (B) lick cluster size, and (C) initial lick rate (total licks during the first 3 min following the first lick). Figure is redrawn from Lin, Arthurs, et al. (2012)

Cunningham, 1979; Cunningham & Noble, 1992; Davies & Parker, 1990; Heinrichs et al., 1998; Jorenby, Steinpreis, Sherman, & Baker, 1990; Mallet & Beninger, 1998; Parker & Gillies, 1995; Sherman, Hickis, Rice, Rusiniak, & Garcia, 1983; Steigerwald, Rusiniak, Eckel, & O'Regan, 1988). However, as appealing as this simple, biphasic view of the behavioral effects of drugs may be, additional caveats are required. For many drugs, first time use is an aversive experience. Taking tobacco as an example, for most smokers their initial experience was not euphoric. Instead, it is often reported that the first exposure to cigarettes makes smokers nauseous and dizzy (e.g., Balfour, 1990; Eissenberg & Balster, 2000). This initial aversive experience is also evident with alcohol and caffeine (e.g., Haertzen, Hooks, & Ross, 1981; Haertzen, Kocher, & Miyasato, 1983). A similar problem is encountered in the clinic, where, for instance, the dose of opioid pain relievers (e.g., morphine) needs to be carefully titrated (beginning at less than 10 mg, for morphine) because patients new to such medication often experience nausea and vomiting (Hirayama, Ishii, Yago, & Ogata, 2001; H. S. Smith, Smith, & Seidner, 2012). Indeed, people experience aversive effects after the administration of a wide range of clinical prescribed and illegal drugs, including amphetamine, barbituates, benzodiazepines, cocaine, heroin, oxycodone, PCP (phencyclidine), MDMA (3,4-methylenedioxymethamphetamine), methamphetamine, and LSD (lysergic acid diethylamide) (e.g., Derlet, Rice, Horowitz, & Lord, 1989; Knollman, Chabner, & Brunton, 2011; Osterhoudt & Penning, 2011; Quinton & Yamamoto, 2006; Showalter & Thornton, 1977; Strassman, 1984; S. R. White, 2002).

Despite the foregoing evidence, it is nonetheless regularly claimed that the CTAs induced with rewarding doses of drugs are a paradox. That is, how could a drug that supports conditioned place preference also support CTA? The two behaviors are claimed to be mutually exclusive—it must be one or the other, but not both. This argument is based on the implicit assumption that the forms of learning underlying each type of effect—conditioned place preference and CTA—are equivalent. However, no such equivalency exists. For CTA, the individual eats a novel substance, and the drug is then administered. That is, CTA involves the sequential exposure to a taste CS followed by a drug US in a situation that engages the feeding system. For conditioned place preference, on the other hand, the drug is administered to an individual before placement in a distinctive chamber of a place-learning apparatus. A conditioned place preference is acquired if the individual, when given a free choice between the drug-paired chamber and a neutral (or novel) chamber, spends more time in the former than the latter. That is, in conditioned place preference, the CS and US are experienced simultaneously (for reviews, see Bardo, Rowlett, & Harris, 1995; Bevins & Cunningham, 2006; Tzschentke, 1998, 2007). Of particular importance to the present analysis, numerous examples have shown that if the place CS is experienced before the drug US (i.e., US administration occurs following removal from the CS chamber and immediately prior to return to the home environment), a conditioned place aversion can be acquired (e.g., Cunningham, Henderson, & Bormann, 1998; Cunningham, Okorn, & Howard, 1997; Cunningham, Smith, & McMullin, 2003; Fudala & Iwamoto, 1987, 1990; Wall, Hinson,

Schmidt, Johnston, & Streather, 1990). These place-learning results show that drugs of abuse have at least two properties (positive and negative), and that which property is expressed in performance can be determined by procedural factors (e.g., temporal order). From this perspective, then, it is neither surprising nor unexpected that drugs of abuse should support CTA learning.

In finishing, we would draw attention to a feature of the CTA mechanism that often is not discussed but that, we believe, is critically important for survival: To be effective, the mechanism must be engaged sooner rather than later. Here is the crux of the issue. The mechanism cannot wait for clear and unambiguous evidence that a poison has entered the internal milieu. To do so would be to gamble with your well-being, and possibly your life. Rather, the earliest-onset signs of a poison must trigger the mechanism. But what does such evidence look like? Presumably, the early-onset signs differ from poison to poison. But, again, how does the mechanism "know" what is evidence of poison if it cannot afford to wait for confirmation that the integrity of the internal milieu has been compromised? The answer, of course, is that such specific information is not needed. In the context of the ingestion of a new food, taste neophobia has primed the feeding system such that a negative deviation of internal well-being or the onset of a novel body state will be sufficient to activate the CTA mechanism. As we previously noted, the price of a CTA mechanism that is triggered by early-onset signs is the occurrence of false positives. This is the price of survival in the world in which the CTA mechanism evolved, a world that did not include drugs of abuse. Although their negative properties may be entirely responsible for CTAs induced by drugs of abuse, it is possible that some early-onset signs of their positive properties could, mistakenly, be taken as evidence of poisoning, and thereby contribute to the acquisition of the inevitable CTA.[6] In other situations (e.g., conditioned place preference, self-administration), the same drug effects are not interpreted as signs of poisoning, because they do not follow consumption of a novel food. Thus, taste neophobia and CTA are exquisitely developed, if somewhat blunt, mechanisms of self-defense. Furthermore, some perplexing issues in the literature, such as CTAs induced by "rewarding" drugs, can be appreciated as the inevitable result of a highly sensitive system, and perhaps a short-circuiting of a basic learning mechanism, rather than as a paradox in need of solving.

[6] This false-positive tendency may account for recent findings that drug-induced CTA serves as a predictor of later self-administration (e.g., Colechio, Imperio, & Grigson, 2014); that is, animals that are more sensitive to the rewarding aspects of the drug may form stronger CTAs if those properties function as early-onset signs of poisoning. On the other hand, in later self-administration sessions, when a taste cue is absent, this sensitivity to drug reward may produce stronger self-administration behavior.

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